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***Mergent Compan Snaphot (File 556)
***Mergent Compan New Report (File 557)
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4/3,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10355631 99458346 PMID: 10530763
Inhibitory effect of mimosine on proliferation of human lung cancer cells is mediated by multiple mechanisms.
Chang HC; Lee TH; Chuang LY; Yen MH; Hung WC
Department of Physiology, Kaohsiung Medical College, Taiwan.
Cancer letters (IRELAND) Oct 18 **1999**, 145 (1-2) p1-8, ISSN 0304-3835 Journal Code: CMX
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The **plant** amino acid mimosine has been reported to block cell cycle progression in the late G1 phase. A recent study showed that mimosine might induce growth arrest by activating the expression of p21CIP1, a cyclin-dependent kinase **inhibitor** (CDKI), and by **inhibiting** the activity of cyclin E-associated kinases in human breast cancer cells. However, mimosine at higher concentrations also blocked proliferation of **p21** -/- cells by unknown mechanisms. In this study, we investigated the effect of mimosine on the expression of cyclins and CDKIs in human lung cancer cells. We found that mimosine specifically **inhibited** cyclin D1 expression in H226 cells. The expression of another G1 cyclin, cyclin E, was not regulated by mimosine in all lung cancer cell lines examined. Moreover, mimosine induced p21CIP1 expression in H226 and H358 cells, while

it activated p27KIP1 expression in H322 cells. However, mimosine does not affect transcription of these genes directly because significant changes in cyclin D1 or CDKI expression were observed at 12-24 h after drug addition. Our results indicate that mimosine may block cell proliferation by multiple mechanisms and this amino acid is a useful agent for the study of cell cycle control.

4/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10342048 99384075 PMID: 10452995
Bromelain, from pineapple stems, proteolytically blocks activation of extracellular regulated kinase-2 in T cells.
Mynott TL; Ladhams A; Scarmato P; Engwerda CR
Department of Biochemistry, Imperial College of Science, Technology and Medicine, London, United Kingdom. t.mynott@ic.ac.uk
Journal of immunology (UNITED STATES) Sep 1 **1999**, 163 (5) p2568-75, ISSN 0022-1767 Journal Code: IFB
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Recently, it has emerged that extracellular proteases have specific regulatory roles in modulating immune responses. Proteases may act as signaling molecules to activate the Raf-1/extracellular regulated kinase (ERK)-2 pathway to participate in mitogenesis, apoptosis, and cytokine production. Most reports on the role of protease-mediated cell signaling, however, focus on their stimulatory effects. In this study, we show for the first time that extracellular proteases may also block signal transduction. We show that bromelain, a mixture of cysteine proteases from pineapple stems, blocks activation of ERK-2 in Th0 cells stimulated via the TCR with anti-CD3epsilon mAb, or stimulated with combined PMA and calcium ionophore. The **inhibitory** activity of bromelain was dependent on its proteolytic activity, as ERK-2 **inhibition** was abrogated by E-64, a selective cysteine protease **inhibitor**. However, **inhibitory** effects were not caused by nonspecific proteolysis, as the protease trypsin had no effect on ERK activation. Bromelain also **inhibited** PMA-induced IL-2, IFN-gamma, and IL-4 mRNA accumulation, but had no effect on TCR-induced cytokine mRNA production. This data suggests a critical requirement for ERK-2 in PMA-induced cytokine production, but not TCR-induced cytokine production. Bromelain did not act on ERK-2 directly, as it also **inhibited** p21ras activation, an effector molecule upstream from ERK-2 in the Raf-1/MEK/ERK-2 kinase signaling cascade. The results indicate that bromelain is a novel **inhibitor** of T cell signal transduction and suggests a novel role for extracellular proteases as **inhibitors** of intracellular signal transduction pathways.

4/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10065757 99175863 PMID: 10076567
Growth **inhibition** of A549 human lung adenocarcinoma cells by L-canavanine is associated with **p21**/WAF1 induction.
Ding Y; Matsukawa Y; OhtaniFujita N; Kato D; Dao S; Fujii T; Naito Y; Yoshikawa T; Sakai T; Rosenthal GA
Department of Preventive Medicine, Kyoto Prefectural University of Medicine.
Japanese journal of cancer research (JAPAN) Jan **1999**, 90 (1) p69-74, ISSN 0910-5050 Journal Code: HBA
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
L-Canavanine (CAV) is a higher **plant** nonprotein amino acid and a potent L-arginine antimetabolite. CAV can **inhibit** the proliferation

of tumor cells in vitro and in vivo, but little is known regarding the molecular mechanisms mediating these effects. We demonstrated that the treatment of human lung adenocarcinoma A549 cells with CAV caused growth **inhibition** ; G1 phase arrest is accompanied by accumulation of an incompletely phosphorylated form of the retinoblastoma protein, whose phosphorylation is necessary for cell cycle progression from G1 to S phase. In addition, CAV induces the expression of p53 and subsequent expression of a cyclin-dependent kinase **inhibitor**, **p21** /WAF1. The p53-dependent induction of **p21** /WAF1 and the following dephosphorylation of the retinoblastoma protein by CAV could account for the observed CAV-mediated G1 phase arrest.

4/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09933969 99009264 PMID: 9790949
Genistein induces **p21**(Cip1/WAF1) expression and blocks the G1 to S phase transition in mouse fibroblast and melanoma cells.
Kuzumaki T; Kobayashi T; Ishikawa K
Department of Biochemistry, Yamagata University School of Medicine, Yamagata, 990-9585, Japan. kuzumaki@med.id.yamagata-u.ac.jp
Biochemical and biophysical research communications (UNITED STATES) Oct 9 **1998**, 251 (1) p291-5, ISSN 0006-291X Journal Code: 9Y8
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Genistein, the principal isoflavonoid in soybeans, is reported to **inhibit** cell cycle progression, but the molecular basis for this event is unknown. Here we show that genistein **inhibits** DNA synthesis and suppresses cyclin E-associated cyclin-dependent kinase-2 (CDK2) activity when quiescent BALB/c 3T3 fibroblasts are stimulated with serum. In these cells, a CDK2 **inhibitor**, **p21**(Cip1/WAF1), is markedly increased by genistein, but another CDK2 **inhibitor**, p27(Kip1), is not increased. In exponentially growing BALB/c 3T3 cells, genistein **inhibits** proliferation of the cells in a dose-dependent manner. Flow cytometric analysis and measurement of DNA synthesis indicate that genistein blocks the G1 to S phase transition of these cells, which is concomitant with G2-M arrest. In mouse B16-F1 melanoma cells, genistein also blocks the transition of G1 to S phase without arresting at G2-M at low doses. In both cell lines, genistein suppresses cyclin E/CDK2 activity and induces **p21** (Cip1/WAF1) expression. These results suggest that genistein affects the restriction point control of the cell cycle by inducing **p21** (Cip1/WAF1) expression in mouse fibroblast and melanoma cells. Copyright 1998 Academic Press.

4/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09928248 98438697 PMID: 9765153
Role of farnesyltransferase in ABA regulation of guard cell anion channels and **plant** water loss.
Pei ZM; Ghassemian M; Kwak CM; McCourt P; Schroeder JI
Department of Biology and Center for Molecular Genetics, University of California, San Diego, La Jolla, CA 92093-0116, USA.
Science (UNITED STATES) Oct 9 **1998**, 282 (5387) p287-90, ISSN 0036-8075 Journal Code: UJ7
Comment in Science. 1998 Oct 9;282(5387) 252-3
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Desiccation of **plants** during drought can be detrimental to agricultural production. The phytohormone abscisic acid (ABA) reduces water loss by triggering stomatal pore closure in leaves, a process requiring

ion-channel modulation by cytoplasmic proteins. Deletion of the Arabidopsis farnesyltransferase gene ERA1 or application of farnesyltransferase **inhibitors** resulted in ABA hypersensitivity of guard cell anion-channel activation and of stomatal closing. ERA1 was expressed in guard cells. Double-mutant analyses of era1 with the ABA-insensitive mutants abi1 and abi2 showed that era1 suppresses the ABA-insensitive phenotypes. Moreover, era1 **plants** exhibited a reduction in transpirational water loss during drought treatment.

4/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09912894 99019317 PMID: 9804172
Promoter activation and following induction of the **p21**/WAF1 gene by flavone is involved in G1 phase arrest in A549 lung adenocarcinoma cells.
Bai F; Matsui T; Ohtani-Fujita N; Matsukawa Y; Ding Y; Sakai T
Department of Preventive Medicine, Kyoto Prefectural University of Medicine, Japan.
FEBS letters (NETHERLANDS) Oct 16 **1998**, 437 (1-2) p61-4, ISSN 0014-5793 Journal Code: EUH
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Flavonoids are present in many **plants** including edible fruits and vegetables. Recently, many of the biological activities of flavonoids have been elucidated. Flavone is a well known flavonoid, and many of its derivatives have been shown to have anti-proliferative effects on several cancer cells. We report here that flavone can effectively **inhibit** the cell growth of human lung adenocarcinoma A549 cells in a dose-dependent manner, and 100 microM flavone causes cell cycle arrest at the G1 phase. As a mechanism underlying the cell cycle arrest, flavone markedly increases the mRNA and protein levels of a universal **inhibitor** of cyclin-dependent kinase, **p21**/WAF1, and **inhibits** phosphorylation of retinoblastoma (RB) protein. Although A549 cells possess wild-type p53, flavone does not induce the p53 protein, suggesting that **p21**/WAF1 induction is p53-independent. In addition, 100 microM flavone significantly increases the promoter activity of the **p21**/WAF1 gene by 5-fold. These results suggest that the G1 phase arrest by flavone is due to p53-independent transcriptional induction of the **p21**/WAF1 gene and the subsequent dephosphorylation of RB protein.

4/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09517859 96321346 PMID: 8759161
Lupane derivatives from Lophopetalum wallichii with farnesyl protein transferase **inhibitory** activity.
Sturm S; Gil RR; Chai HB; Ngassapa OD; Santisuk T; Reutrakul V; Howe A; Moss M; Besterman JM; Yang SL; Farthing JE; Tait RM; Lewis JA; O'Neill MJ; Farnsworth NR; Cordell GA; Pezzuto JM; Kinghorn AD
Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago 60612, USA.
Journal of natural products (UNITED STATES) Jul **1996**, 59 (7) p658-63, ISSN 0163-3864 Journal Code: JA4
Contract/Grant No.: U01-CA52956, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Chloroform-soluble extracts of the stems and of the mixed stems and stem bark of Lophopetalum wallichii were found to be **inhibitory** in a farnesyl protein transferase (FPTase) bioassay system. During the course of activity-guided fractionation, the known lupane-type triterpenes, ochraceolide A (1), ochraceolide B (2), betulin, and lupeol and the new

lupane lactone, dihydro ochraceolide A (4), were isolated. The stereochemistry of the epoxide group of ochraceolide B was determined by preparation of both epoxide isomers [2, and the new semisynthetic derivative, 20-epi-ochraceolide B (3)] from 1. The structure of 4 was established by reduction of 1 with sodium borohydride. Compounds 1 and 2 exhibited significant **inhibitory** activity in the FPTase assay (IC50 values of 1.0 and 0.7 microgram/mL, respectively). Lupeol was found to be weakly active (IC50 65.0 micrograms/mL) in this test system, whereas no significant **inhibition** was detected for betulin or compounds 3 or 4. When evaluated against a panel of human cancer cells in culture, compounds 1 and 4 were modestly cytotoxic. Compounds 2 and 3 were not active in the panel.

4/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09466899 97354727 PMID: 9210954

Induction of **p21** /WAF1 and G1 cell-cycle arrest by the chemopreventive agent apigenin.

Lepley DM; Pelling JC

Eppley Institute for Cancer Research, University of Nebraska Medical Center, Omaha, USA.

Molecular carcinogenesis (UNITED STATES) Jun **1997**, 19 (2) p74-82, ISSN 0899-1987 Journal Code: AEQ

Contract/Grant No.: CA71041, CA, NCI; CA72987, CA, NCI

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Apigenin is a **plant** flavonoid that has been shown to significantly **inhibit** ultraviolet-induced mouse skin tumorigenesis when applied topically and may be an alternative sunscreen agent for humans. A long-term goal of our laboratory is to elucidate the molecular mechanism or mechanism by which apigenin **inhibits** skin tumorigenesis. In a previous publication, we characterized the mechanism by which apigenin induced G2/M arrest in keratinocytes. More recent studies in our laboratory have provided evidence that apigenin can induce G1 arrest in addition to arresting cells at G2/M. Here we describe the mechanism of the apigenin-induced G1 arrest in human diploid fibroblasts (HDF). Treatment of asynchronous HDF for 24 h with 10-50 microM apigenin resulted in dose-dependent cell-cycle arrest at both the G0/G1 and G2/M phases as measured by flow cytometry. The G0/G1 arrest was more clearly defined by using HDF that were synchronized in G0 and then released from quiescence by replating at subconfluent densities in medium containing 10-70 microM apigenin. The cells were analyzed for cell-cycle progression or cyclin D1 expression 24 h later. A dose of apigenin as low as 10 microM reduced the percentage of cells in S phase by 20% compared with control cultures treated with solvent alone. Western blot analysis of apigenin-treated HDF indicated that cyclin D1 was expressed at higher levels than in untreated cells, which signifies that they were arrested in G1 phase rather than in a G0 quiescent state. The G1 arrest was further studied by cyclin-dependent kinase 2 (cdk2) immune complex-kinase assays of apigenin-treated asynchronous HDF, which demonstrated a dose-dependent **inhibition** of cdk2 by apigenin. **Inhibition** of cdk2 kinase activity in apigenin-treated cells was associated with the accumulation of the hypophosphorylated form of the retinoblastoma (Rb) protein as measured by western blot analysis. The cdk **inhibitor p21**/WAF1 was also induced in a dose-dependent manner, with a 22-fold induction of **p21** /WAF1 in 70 microM apigenin-treated cells. In conclusion, apigenin treatment produced a G1 cell-cycle arrest by **inhibiting** cdk2 kinase activity and the phosphorylation of Rb and inducing the cdk **inhibitor p21**/WAF1, all of which may mediate its chemopreventive activities in vivo. To our knowledge this is the first report of a chemopreventive agent inducing **p21** /WAF1, a known downstream effector of the p53 tumor suppressor protein.

4/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09122419 97143882 PMID: 8989889
Protein farnesyltransferase in **plants**: molecular characterization and involvement in cell cycle control.
Qian D; Zhou D; Ju R; Cramer CL; Yang Z
Department of Plant Biology, Ohio State University, Columbus 43210, USA.
Plant cell (UNITED STATES) Dec **1996**, 8 (12) p2381-94, ISSN 1040-4651 Journal Code: BJU
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Farnesylation is required for membrane targeting, protein-protein interactions, and the biological activity of key regulatory proteins, such as Ras small GTPases and protein kinases in a wide range of eukaryotes. In this report, we describe the molecular identification of a **plant** protein farnesyltransferase (FTase) and evidence for its role in the control of the cell cycle in **plants**. A pea gene encoding a homolog of the FTase beta subunit was previously cloned using a polymerase chain reaction-based strategy. A similar approach was used to clone a pea gene encoding a homolog of the FTase alpha subunit. The biochemical function of the pea FTase homologs was demonstrated by the reconstitution of FTase enzyme activity using FTase fusion proteins coexpressed in Escherichia coll. RNA gel blot analyses showed that levels of FTase mRNAs are generally higher in tissues, such as those of nodules, that are active in cell division. The relationship of FTase to cell division was further analyzed during the growth of suspension-cultured tobacco BY-2 cells. A biphasic fluctuation of FTase enzyme activity preceded corresponding changes in mitotic activity at the early log phase of cell growth. Moreover, manumycin, a specific **inhibitor** of FTase, was effective in **inhibiting** mitosis and growth in these cells. Using synchronized BY-2 cells, manumycin completely blocked mitosis when added at the early S phase but not when added at the G2 phase. These data suggest that FTase is required for the **plant** cell cycle, perhaps by modulating the progression through the S phase and the transition from G1 to the S phase.

4/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08899032 95352094 PMID: 7626110
Reversion of v-H-ras-transformed NIH 3T3 cells by apigenin through **inhibiting** mitogen activated protein kinase and its downstream oncogenes.
Kuo ML; Yang NC
Institute of Toxicology, College of Medicine, National Taiwan University, Taipei, Republic of China.
Biochemical and biophysical research communications (UNITED STATES) Jul 26 **1995**, 212 (3) p767-75, ISSN 0006-291X Journal Code: 9Y8
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Apigenin, a **plant** flavonoid, induced the reversion of transformed phenotypes of v-H-ras-transformed NIH 3T3 cells at a quite low concentration of 12.5 microM. In the present study, we have examined the components of this Ras-mediated signaling transduction to determine whether they were involved in the apigenin-induced reversion process. Interestingly, the consitutively activated mitogen activated protein kinase (MAPK) in the ras transformant was **inhibited** significantly and rapidly by 25 microM apigenin within 30 min, and this reduction continued for more than 4 h. Corroborating these observations, expression of the downstream oncogenes c-jun and c-fos was also dramatically reduced during

the first 4 h of treatment. We found that the levels of ras protein and mRNA were not affected [redacted] 24 h of treatment with apigenin. These findings indicate that apigenin-induced reversion of v-H-ras-transformed NIH 3T3 cells may occur by **inhibiting** MAPK activity and its downstream oncogenes rather than by affecting the expression of the ras gene.

4/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08709171 96163453 PMID: 8575428
Identification of spinach farnesyl protein transferase. Dithiothreitol as an acceptor in vitro.
Parmryd I; Shipton CA; Swiezewska E; Andersson B; Dallner G
Arrhenius Laboratories for Natural Sciences, Biochemistry Department, Stockholm University, Sweden.
European journal of biochemistry (GERMANY) Dec 15 **1995**, 234 (3) p723-31, ISSN 0014-2956 Journal Code: EMZ
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Spinach seedlings were found to contain farnesyl protein transferase. The enzyme is activated by Zn2+, but not by Mg2+. The pH optimum is approximately 7.0 and maximal activity is obtained at 40-45 degrees C. The apparent Km for the farnesyl diphosphate substrate is 7 microM. Western blotting of soluble proteins with an antiserum raised against mammalian farnesyl protein transferase demonstrated a specific cross-reactivity with the spinach enzyme. The antiserum preferentially recognises the beta-subunit of the heterodimeric farnesyl protein transferase, and the corresponding spinach polypeptide has a molecular mass of 42 kDa on SDS/PAGE. The enzyme can employ dithiothreitol as an acceptor for the farnesyl moiety and catalyses the formation of a thioether linkage between these substrates. On the basis of this discovery, a new method was developed utilising the hydrophobicity of the reaction product, and its interaction with poly(propylene). During in vivo labelling, the **plants** took up dithiothreitol, which **inhibited** the incorporation of [3H]mevalonate metabolites into proteins, indicating that dithiothreitol might be isoprenylated in vivo as well as in vitro. However, isoprenylation of some proteins remains unaffected by dithiothreitol suggesting the existence of different isoprenylation mechanisms. Thus, it is demonstrated that **plants** possess farnesyl protein transferase, which resembles its mammalian and yeast homologues.

4/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07887964 93250434 PMID: 8485402
Protein isoprenylation in suspension-cultured tobacco cells.
Randall SK; Marshall MS; Crowell DN
Department of Biology, Indiana University-Purdue University, Indianapolis 46202-5132.
Plant cell (UNITED STATES) Apr **1993**, 5 (4) p433-42, ISSN 1040-4651 Journal Code: BJU
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Many mammalian and yeast proteins, including small ras-like GTP binding proteins, heterotrimeric G protein gamma subunits, and nuclear lamins, have been shown to be covalently linked to isoprenoid derivatives of mevalonic acid. Isoprenylation of these proteins is required for their assembly into membranes and, hence, for their biological activity. In this report, it is shown that cultured tobacco cells, when pretreated with an **inhibitor** of endogenous mevalonic acid synthesis (lovastatin), incorporate radioactivity from 14C-mevalonic acid into proteins. Most of these proteins

are membrane associated, and many are similar in mass to mammalian ras-like GTP binding proteins and nuclear lamins. Furthermore, it is shown that tobacco cell extracts catalyze the transfer of radioactivity from 3H-farnesyl pyrophosphate and 3H-geranylgeranyl pyrophosphate to protein substrates in vitro. These studies indicate the presence of at least two distinct prenyl:protein transferases in tobacco extracts: one that utilizes farnesyl pyrophosphate and preferentially modifies a substrate protein with a CAIM carboxy terminus (farnesyl:protein transferase) and one that utilizes geranylgeranyl pyrophosphate and preferentially modifies a substrate protein with a CAIL carboxy terminus (geranylgeranyl:protein transferase type I). This work provides a basis for future work on the role of protein isoprenylation in **plant** cell growth, signal transduction, and membrane biogenesis.

4/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07829994 91160723 PMID: 2001736
The three-dimensional structure of the bifunctional proteinase K/alpha-amylase **inhibitor** from wheat (PK13) at 2.5 A resolution.
Zemke KJ; Muller-Fahrnow A; Jany KD; Pal GP; Saenger W
Institut fur Kristallographie, Freie Universitat Berlin, Germany.
FEBS letters (NETHERLANDS) Feb 25 **1991**, 279 (2) p240-2, ISSN 0014-5793 Journal Code: EUH
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Wheat germ contains an **inhibitor** for proteinase K, called PK13 (Mr approximately 19,600) which simultaneously **inhibits** alpha-amylase. PK13 was crystallized, space group **P21**, a = 43.02 (5) A, b = 65.18 (7) A, c = 32.33 (4) A, beta = 112.79 degrees (9), X-ray data were collected to 2.5 A resolution, the structure solved by molecular replacement on the basis of the atomic coordinates of the homologous Erythrina caffra DE-3 **inhibitor**, and refined with simulated annealing techniques with a current R-factor of 21%. The three-dimensional structure of PK13 is stabilised by two disulfide bridges and has a central beta-barrel with distorted beta-structure. In analogy to related **inhibitors** , the binding site for proteinase K is assumed to be located on the surface of the protein (amino acid residues 66-67), although the 75-76 peptide bond is cleaved upon binding.

4/3,AB/14 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12322142 BIOSIS NO.: 200000075644
Direct activation of the fission yeast PAK Shk1 by the novel SH3 domain protein, Skb5.
AUTHOR: Yang Peirong; Pimental Ruth; Lai Hong; Marcus Stevan(a)
AUTHOR ADDRESS: (a)Department of Molecular Genetics, University of Texas M. D. Anderson Cancer Center, Houston, TX**USA
JOURNAL: Journal of Biological Chemistry 274 (51):p36052-36057 Dec. 17, **1999**
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The **p21**-activated kinase (PAK) homolog Shk1 is essential for cell viability in the fission yeast Schizosaccharomyces pombe. Roles have been established for Shk1 in the regulation of cell morphology, sexual differentiation, and mitosis in S. pombe. In this report, we

describe the genetic and molecular characterization of a novel SH3 domain protein, Skb5, identified as a result of a two-hybrid screen for Shk1 interacting proteins. S. pombe cells carrying a deletion of the skb5 gene exhibit no discernible phenotypic defects under normal growth conditions, but when subjected to hypertonic stress, become spheroidal in shape and growth impaired. Both of these defects can be suppressed by overexpression of the Shk1 modulator, Skb1. The growth **inhibition** that results from overexpression of Shk1 in S. pombe cells is markedly suppressed by a null mutation in the skb5 gene, suggesting that Skb5 contributes positively to the function of Shk1 in vivo. Consistent with this notion, we show that Skb5 stimulates Shk1 catalytic function in S. pombe cells. Furthermore, and perhaps most significantly, we show that bacterially expressed recombinant Skb5 protein directly stimulates the catalytic activity of recombinant Shk1 kinase in vitro. These and additional data described herein demonstrate that Skb5 is a direct activator of Shk1 in fission yeast.

1999

4/3,AB/15 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12284254 BIOSIS NO.: 200000042121
Human JIK, a novel member of the STE20 kinase family that **inhibits** JNK and is negatively regulated by epidermal growth factor.
AUTHOR: Tassi Elena; Biesova Zuzanna; Di Fiore Pier Paolo; Gutkind J Silvio (a); Wong William T
AUTHOR ADDRESS: (a)Oral and Pharyngeal Cancer Branch, NIDCR, National Institutes of Health, Bethesda, MD, 20892-4330**USA
JOURNAL: Journal of Biological Chemistry 274 (47):p33287-33295 Nov. 19, **1999**
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Mammalian members related to Saccharomyces cerevisiae serine/threonine kinase STE20 can be divided into two subfamilies based on their structure and function. The PAK subfamily is characterized by an N-terminal **p21**-binding domain (also known as CRIB domain), a C-terminal kinase domain, and is regulated by the small GTP-binding proteins Rac1 and Cdc42Hs. The second group is represented by the GCK-like members, which contain an N-terminal catalytic domain and lack the **p21**-binding domain. Some of them have been demonstrated to induce c-Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK) cascade, while others have been shown to be activated by a subset of stress conditions or apoptotic agents, although little is known about their specific function. Here, we have identified a novel human STE20-related serine/threonine kinase, belonging to the GCK-like subfamily. This kinase does not induce the JNK/SAPK pathway, but, instead, **inhibits** the basal activity of JNK/SAPK, and diminishes its activation in response to human epidermal growth factor (EGF). Therefore, we designated this molecule JIK for JNK/SAPK-**inhibitory** kinase. The **inhibition** of JNK/SAPK signaling pathway by JIK was found to occur between the EGF receptor and the small GTP-binding proteins Rac1 and Cdc42Hs. In contrast, JIK does not activate nor does it **inhibit** ERK2, ERK6, p38, or ERK5. Furthermore, JIK kinase activity is not modulated by any exogenous stimuli, but, interestingly, it is dramatically decreased upon EGF receptor activation. Thus, JIK might represent the first member of the STE20 kinase family whose activity can be negatively regulated by tyrosine kinase receptors, and whose downstream targets **inhibit**, rather than enhance, JNK/SAPK

activation.
1999

4/3,AB/16 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12273086 BIOSIS NO.: 200000026588
Crystallization and preliminary X-ray diffraction studies of a Bowman-Birk **inhibitor** from Vigna unguiculata seeds.
AUTHOR: Rao K N; Hegde S S; Lewis R J; Suresh C G(a)
AUTHOR ADDRESS: (a)Division of Biochemical Sciences, National Chemical Laboratory, Pune, 411008**India
JOURNAL: Acta Crystallographica Section D Biological Crystallography 55 (11):p1920-1922 Nov., **1999**
ISSN: 0907-4449
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: A Bowman-Birk type trypsin/chymotrypsin **inhibitor** isolated from Vigna unguiculata seeds has been crystallized. Crystals were grown using the vapour-diffusion method at pH 4.0 using citrate/phosphate as a buffer and 30% saturated ammonium sulfate as precipitant. The crystals belonged to the monoclinic space group **P21**, with unit-cell parameters a = 32.4, b = 61.8, c = 32.9 ANG, beta = 114.5degree. The Matthews coefficient calculated assuming two molecules in the asymmetric unit was 1.95 ANG3 Da-1, which corresponds to a 37% solvent content. X-ray data were collected to 2.5 ANG resolution from a flash-frozen crystal. The structure was solved using the molecular-replacement method using tracy soybean **inhibitor** structure (PDB entry 1pi2) as a model.

1999

4/3,AB/17 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12260591 BIOSIS NO.: 200000014093
Reciprocal signaling between heterotrimeric G proteins and the **p21** -stimulated protein kinase.
AUTHOR: Wang Jun; Frost Jeffrey A; Cobb Melanie H; Ross Elliott M(a)
AUTHOR ADDRESS: (a)Dept. of Pharmacology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX, 75235-9041**USA
JOURNAL: Journal of Biological Chemistry 274 (44):p31641-31647 Oct. 29, **1999**
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: **p21**-activated protein kinase (PAK)-1 phosphorylated Galphaz, a member of the Galphai family that is found in the brain, platelets, and adrenal medulla. Phosphorylation approached 1 mol of phosphate/mol of Galphaz in vitro. In transfected cells, Galphaz was phosphorylated both by wild-type PAK1 when stimulated by the GTP-binding protein Rac1 and by constitutively active PAK1 mutants. In vitro, phosphorylation occurred only at Ser16, one of two Ser residues that are the major substrate sites for protein kinase C (PKC). PAK1 did not phosphorylate other Galpha subunits (i1, i2, i3, o, s, or q).

PAK1-phosphorylated Galphaz was resistant both to RGSZ1, a Gz-selective GTPase-activating protein (GAP), and to RGS4, a relatively non-selective GAP for the Gi and Gq families of G proteins. Phosphorylation of Ser27 by PKC did not alter sensitivity to either GAP. The previously described **inhibition** of Gz GAPs by PKC is therefore mediated by phosphorylation of Ser16. Phosphorylation of either Ser16 by PAK1 or Ser27 by PKC decreased the affinity of Galphaz for Gbetagamma; phosphorylation of both residues by PKC caused no further effect. PAK1 thus regulates Galphaz function by attenuating the **inhibitory** effects of both GAPs and Gbetagamma. In this context, the kinase activity of PAK1 toward several protein substrates was directly **inhibited** by Gbetagamma, suggesting that PAK1 acts as a Gbetagamma-regulated effector protein. This **inhibition** of mammalian PAK1 by Gbetagamma contrasts with the stimulation of the PAK homolog Ste20p in Saccharomyces cerevisiae by the Gbetagamma homolog Ste4p/Ste18p.

1999

4/3,AB/18 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12072478 BIOSIS NO.: 199900367327
Expression, purification, and characterization of interferon-tau produced in Pichia pastoris grown in a minimal medium.
AUTHOR: Johnson Tonny M; Holaday S Kent; Sun Yahong; Subramaniam Prem S; Johnson Howard M; Krishna N Rama(a)
AUTHOR ADDRESS: (a)Comprehensive Cancer Center, University of Alabama at Birmingham, CHSB-19 B-31, NMR Core Facilit**USA
JOURNAL: Journal of Interferon and Cytokine Research 19 (6):p631-636 June, **1999**
ISSN: 1079-9907
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Interferon-tau (IFN-tau) is a novel type I IFN that was originally identified as a pregnancy recognition hormone. IFN-tau shares all of the biological properties of other type I IFNs including antiviral activity and antiproliferative activity through induction of the cell cycle **inhibitor** gene product p21WAF1. It is a promising therapy for cancers, viral infections, and for autoimmune disorders such as multiple sclerosis, without the adverse side effects associated with IFN-alpha and IFN-beta. Here, we describe novel growth and induction conditions for the expression of functionally active and uniformly 15N-labeled IFN-tau from Pichia pastoris in a minimal media for use in initial 2D- and 3D-NMR studies in solution. Purified 15N-IFN-tau was homogenous, as determined by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and MALDI-TOF mass spectrometer (MS), and retained full biological activity. MS analysis confirmed uniform isotopic labeling of IFN-tau with 15N incorporation exceeding 99%. Circular dichroism (CD) as well as 1D-NMR and 15N-1H heteronuclear single quantum coherence (HSQC) spectra confirmed that purified 15N-labeled IFN-tau has a stable secondary structure. Besides providing a route for isotope labeling of IFN-tau, our procedure may be useful for the expression and purification of other proteins that are difficult to obtain in Pichia pastoris grown in minimal media.

1999

4/3,AB/19 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

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12030064 BIOSIS NO.: 199900310583
The Cdc42p GTPase is involved in a G2/M morphogenetic checkpoint regulating the apical-isotropic switch and nuclear division in yeast.
AUTHOR: Richman Tamara J; Sawyer Mathew M; Johnson Douglas I(a)
AUTHOR ADDRESS: (a)Dept. of Microbiology and Molecular Genetics, University of Vermont, 202 Stafford Hall, Burlingt**USA
JOURNAL: Journal of Biological Chemistry 274 (24):p16861-16870 June 11, **1999**
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The Cdc42p GTPase is involved in the signal transduction cascades controlling bud emergence and polarized cell growth in S. cerevisiae. Cells expressing the cdc42V44A effector domain mutant allele displayed morphological defects of highly elongated and multielongated budded cells indicative of a defect in the apical-isotropic switch in bud growth. In addition, these cells contained one, two, or multiple nuclei indicative of a G2/M delay in nuclear division and also a defect in cytokinesis and/or cell separation. Actin and chitin were delocalized, and septin ring structure was aberrant and partially delocalized to the tips of elongated cdc42V44A cells; however, Cdc42V44Ap localization was normal. Two-hybrid protein analyses showed that the V44A mutation interfered with Cdc42p's interactions with Cla4p, a **p21**(Cdc42/Rac)-activated kinase (PAK)-like kinase, and the novel effectors Gic1p and Gic2p, but not with the Ste20p or Skm1p PAK-like kinases, the Bni1p formin, or the Iqg1p IQGAP homolog. Furthermore, the cdc42V44A morphological defects were suppressed by deletion of the Swe1p cyclin-dependent kinase **inhibitory** kinase and by overexpression of Cla4p, Ste20p, the Cdc12 septin protein, or the guanine nucleotide exchange factor Cdc24p. In sum, these results suggest that proper Cdc42p function is essential for timely progression through the apical-isotropic switch and G2/M transition and that Cdc42V44Ap differentially interacts with a number of effectors and regulators.

1999

4/3,AB/20 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

11948749 BIOSIS NO.: 199900194858
Cdc42: An essential Rho-type GTPase controlling eukaryotic cell polarity.
AUTHOR: Johnson Douglas I(a)
AUTHOR ADDRESS: (a)Dep. Microbiol. Mol. Genet., Univ. Vt., 202A Stafford Hall, Burlington, VT 05405**USA
JOURNAL: Microbiology and Molecular Biology Reviews 63 (1):p54-105 March, **1999**
ISSN: 1092-2172
DOCUMENT TYPE: Literature Review
RECORD TYPE: Citation
LANGUAGE: English
1999

4/3,AB/21 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

11827833 BIOSIS NO.: 199900073942

Genetic evidence for Pak1 [redacted]utoinhibition and its release b[redacted]Cdc42.
AUTHOR: Tu Hua; Wigler Mi[redacted](a)
AUTHOR ADDRESS: (a)Cold Springs Harbor Lab., Cold Spring Harbor, NY 11724**
USA
JOURNAL: Molecular and Cellular Biology 19 (1):p602-611 Jan., **1999**
ISSN: 0270-7306
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Pak1 protein kinase of Schizosaccharomyces pombe, a member of the **p21**-GTPase-activated protein kinase (PAK) family, participates in signaling pathways including sexual differentiation and morphogenesis. The regulatory domain of PAK proteins is thought to **inhibit** the kinase catalytic domain, as truncation of this region renders kinases more active. Here we report the detection in the two-hybrid system of the interaction between Pak1 regulatory domain and the kinase catalytic domain. Pak1 catalytic domain binds to the same highly conserved region on the regulatory domain that binds Cdc42, a GTPase protein capable of activating Pak1. Two-hybrid, mutant, and genetic analyses indicated that this intramolecular interaction rendered the kinase in a closed and inactive configuration. We show that Cdc42 can induce an open configuration of Pak1. We propose that Cdc42 interaction disrupts the intramolecular interactions of Pak1, thereby releasing the kinase from autoinhibition.

1999

4/3,AB/22 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11770888 BIOSIS NO.: 199900016997
A budding yeast G1 DNA damage checkpoint requires cyclin-dependent kinase.
AUTHOR: Fitzgerald J N; Kron S J
AUTHOR ADDRESS: Dep. Mol. Gent. Cell Biol., Univ. Chicago, Chicago, IL 60637**USA
JOURNAL: Molecular Biology of the Cell 9 (SUPPL.):p112A Nov., **1998**
CONFERENCE/MEETING: 38th Annual Meeting of the American Society for Cell Biology San Francisco, California, USA December 12-16, 1998
SPONSOR: American Society for Cell Biology
ISSN: 1059-1524
RECORD TYPE: Citation
LANGUAGE: English
1998

4/3,AB/23 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11709067 BIOSIS NO.: 199800490798
The p16INK4A protein and flavopiridol restore yeast cell growth **inhibited** by Cdk4.
AUTHOR: Moorthamer Mark; Panchal Mayur; Greenhalf William; Chaudhuri Bhabatosh(a)
AUTHOR ADDRESS: (a)Oncol. Res., Novartis Pharma AG, K-125.13.17, Basel** Switzerland
JOURNAL: Biochemical and Biophysical Research Communications 250 (3):p 791-797 Sept. 29, **1998**
ISSN: 0006-291X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Cyclin-dependent kinase 4 (Cdk4) activity is mis[redacted]gulated in most cancers. Loss of Cdk4 regulation can occur through overexpression of Cdk4 catalytic subunit or its regulatory partner cyclin D1, or if the Cdk4-specific **inhibitory** protein p16INK4A is inactive. We have attempted to express the two human subunits, Cdk4 and cyclin D1, in the yeast Saccharomyces cerevisiae. Surprisingly, expression of Cdk4 alone, under control of the strong GAL promoter, **inhibits** cell growth. Coexpression of both subunits allows formation of an active Cdk4-cyclin D1 complex which accentuates growth arrest. In cells expressing Cdk4 only, growth is restored by overexpressing human Cdc37, a Cdk4-binding molecular chaperone. Interestingly, the effect of Cdk4 on yeast is also overcome by both p16 and **p21**-families of Cdk-**inhibitory** proteins. Moreover, flavopiridol, a compound which **inhibits** Cdk4 enzyme activity, restores cell division. The fact that p16INK4A and flavopiridol negate Cdk4-mediated suppression of yeast cell growth implies that this simple system can be used as a screen for identifying Cdk4-specific antagonists which may mimic p16INK4A in the cancer cell cycle.

1998

4/3,AB/24 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11703037 BIOSIS NO.: 199800484768
Inhibitory effect of methanol extract of Boschniakia rossica Fedtisch. et Flerov on rat hepatic preneoplastic lesions induced by diethylnitrosamine.
AUTHOR: Zong Zhu-Yin; Hai Liang-Jin(a); Tian Zhu-Li; Jung Joon-Lee(a); Young Ho-Kim; Chul Ho-Lee; Ki Hoon-Lee; Byung Hwa-Hyun
AUTHOR ADDRESS: (a)Biochem. Lab. Cancer Res., Yanbian Univ. Coll. Med., Yanji 133000**China
JOURNAL: Zhongguo Zhongyao Zazhi 23 (7):p424-426, 448-449 July, **1998**
ISSN: 1001-5302
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: Chinese; Non-English
SUMMARY LANGUAGE: Chinese; English

ABSTRACT: Objective: To investigate the **inhibitory** effect of Boschniakia rossica (BR) on hepatocarcinogenesis in rats. Method: Based on immunohistochemistry techniques, the expression of placental form glutathione S-transferase(GST-P), mutant p53 and **p21** protein were investigated in hepatic preneoplastic lesions induced by Solt-Farber protocol in the liver of rats that had been treated with the above method, administered with BR extract and of control group. Result: The extract of BR (500mg/kg) has **inhibitory** effect on the formation of diethylnitrosamine-induced GST-P-positive foci in F344 rat and the expression of mutant p53 and **p21** protein was lower than that of hepatic, preneoplastic lesions, and the increasing gamma-glutamyltranspeptidase (gamma-GT) activity in rat liver treated with Solt-Farber protocol was decreased by the extract of BR. Conclusion: These results indicate that BR has **inhibitory** effect on DEN induced hepatic preneoplastic lesions in F344 rat.

1998

4/3,AB/25 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11697745 BIOSIS NO.: 199800479476
Functional sites of human PCNA which interact with **p21** (Cip1/Waf1), DNA polymerase delta and replication factor C.
AUTHOR: Oku Takashi; Ikeda Soichiro; Sasaki Hisashi; Fukuda Kotaro; Morioka Hiroshi; Ohtsuka Eiko; Yoshikawa Hiroshi; Tsurimoto Toshiki(a)
AUTHOR ADDRESS: (a)Fac. Biol. Sci., Nara Inst. Sci. Technol., Takayama, Ikoma 630-0101**Japan
JOURNAL: Genes to Cells 3 (6):p357-369 June, **1998**
ISSN: 1356-9597
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background: PCNA, an eukaryotic DNA sliding clamp interacts with replication factors and the cell cycle protein, **p21**(Cip1/Waf1) and functions as a molecular switch for DNA elongation. To understand how DNA replication is regulated through PCNA, elucidation of the precise mechanisms of these protein interactions is necessary. Results: Loop-region mutants in which human PCNA sequences were substituted with the corresponding Saccharomyces cerevisiae PCNA regions were prepared. Analysis of their functions, along with previously prepared alanine scanning mutants, demonstrated that some loops interact with DNA polymerase delta (pol delta) and replication factor C (RFC). The **p21** binding sites of PCNA, mapped by affinity measurement of the mutant forms, found to be located within a distinct structure of the PCNA monomer, overlap with RFC- and pol delta-interaction sites. Competition between **p21** and pol delta or R.FC for binding to PCNA results in efficient **inhibition** of its stimulation of pol delta DNA synthesis and RFC ATPase but not of PCNA loading on DNA by RFC. Conclusions: Semi-saturated amounts of **p21** selectively block formation of the active pot delta complex but not the RFC-PCNA complex at 3'-ends of DNA primers. This differential effect may explain the specific **inhibition** of DNA replication by **p21**.

1998

4/3,AB/26 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11492633 BIOSIS NO.: 199800273965
14-3-3sigmad is a p53-regulated **inhibitor** of G2/M progression.
AUTHOR: Hermeking Heiko(a); Lengauer Christoph(a); Polyak Kornelia(a); He Tong-Chuan(a); Zhang Lin(a); Thiagalingam Sam(a); Kinzler Kenneth W(a); Vogelstein Bert(a)
AUTHOR ADDRESS: (a)Johns Hopkins Oncol. Cent., Johns Hopkins Univ. Sch. Med., Baltimore, MD 21231**USA
JOURNAL: Molecular Cell 1 (1):p3-11 Dec., **1997**
ISSN: 1097-2765
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Exposure of colorectal cancer (CRC) cells to ionizing radiation results in a cell-cycle arrest in G1 and G2. The G1 arrest is due to p53-mediated induction of the cyclin-dependent kinase **inhibitor** p21WAF1/CIP1/SDI1, but the basis for the G2 arrest is unknown. Through a quantitative analysis of gene expression patterns in CRC cell lines, we have discovered that 14-3-3sigma is strongly induced by gamma irradiation and other DNA-damaging agents. The induction of 14-3-3sigma is mediated by a p53-responsive element located 1.8 kb upstream of its transcription start site. Exogenous introduction of 14-3-3sigma into cycling cells results in a G2 arrest. As the fission yeast 14-3-3 homologs rad24 and rad25 mediate similar checkpoint effects, these results document a

molecular mechanism for G2/M control that is conserved throughout eukaryotic evolution and regulated in human cells by p53

1997

4/3,AB/27 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11345526 BIOSIS NO.: 199800126858
Crystallization and preliminary crystallographic studies of a new crystal form of papain from Carica papaya.
AUTHOR: Kozak Maciej; Kozian Elzbieta; Grzonka Zbigniew; Jaskolski Mariusz (a)
AUTHOR ADDRESS: (a)Cent. Biocrystallographic Res., Inst. Bioorganic Chem., Polish Acad. Sciences, Z. Noskowskiego 1**Poland
JOURNAL: Acta Biochimica Polonica 44 (3):p601-605 **1997**
ISSN: 0001-527X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A new crystal form of papain from the latex of Carica papaya, complexed with an **inhibitor** (Z-Arg-Leu-Val-Gly-CHN2) was obtained by the vapor-diffusion method using a methanol/ethanol mixture as a precipitant. The slat-like crystals are monoclinic, space group **P21** , with unit cell parameters a = 42.6 ANG, b = 49.8 ANG, c = 50.5 ANG, beta = 111.9degree, and contain one molecule in the asymmetric unit. The crystals are stable in the X-ray beam and diffract beyond 1.8 ANG. A molecular model has been placed in the unit cell by molecular replacement.

1997

4/3,AB/28 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11253245 BIOSIS NO.: 199800034577
X-ray crystallographic studies of Candida albicans dihydrofolate reductase: High resolution structures of the holoenzyme and an **inhibited** ternary complex.
AUTHOR: Whitlow Marc; Howard Andrew J; Stewart David; Hardman Karl D; Kuyper Lee F(a); Baccanari David P; Fling Mary E; Tansik Robert L
AUTHOR ADDRESS: (a)Glaxo Wellcome Inc., Research Triangle Park, NC 27709** USA
JOURNAL: Journal of Biological Chemistry 272 (48):p30289-30298 Nov. 28, **1997**
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The recent rise in systemic fungal infections has created a need for the development of new antifungal agents. As part of an effort to provide therapeutically effective **inhibitors** of fungal dihydrofolate reductase (DHFR), we have cloned, expressed, purified, crystallized, and determined the three-dimensional structure of Candida albicans DHFR. The 192-residue enzyme, which was expressed in Escherichia coli and purified by methotrexate affinity and cation exchange chromatography, was 27% identical to human DHFR. Crystals of C. albicans DHFR were grown as the holoenzyme complex and as a ternary complex containing a pyrroloquinazoline **inhibitor**. Both complexes

crystallized with two molecules in the asymmetric unit in space group **P21**. The final structure had R-factors of 0.199 at 1.85 ANG resolution and 0.155 at 1.60-ANG resolution, respectively. The enzyme fold was similar to that of bacterial and vertebrate DHFR, and the binding of a nonselective diaminopyrroloquinazoline **inhibitor** and the interactions of NADPH with protein were typical of ligand binding to other DHFRs. However, the width of the active site cleft of C. albicans DHFR was significantly larger than that of the human enzyme, providing a basis for the design of potentially selective **inhibitors**.

1997

4/3,AB/29 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11164151 BIOSIS NO.: 199799785296
Linking protein kinase C to cell-cycle control.
AUTHOR: Livneh Etta(a); Fishman Daniel D
AUTHOR ADDRESS: (a)Dep. Immunol. Microbiol., Fac. Health Sci., Ben Gurion Univ., IL-84105 Beer Sheva**Israel
JOURNAL: European Journal of Biochemistry 248 (1):p1-9 **1997**
ISSN: 0014-2956
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Protein kinase C (PKC) isoenzymes are involved in diverse cellular functions, including differentiation, growth control, tumor promotion, and cell death. In recent years, evidence has began to emerge suggesting a role for PKC in cell cycle control. A paper published recently, demonstrating a functional link between PKC and cell cycle control in yeast (Marini, N. J., Meldrum, E., Buehrer, B., Hubberstey, A. V., Stone, D. E., Traynor-Kaplan, A. & Reed, S. I. (1996) EMBO J. 15, 3040-3052), strengthens this data. Thus, the existence of cell-cycle-regulated pathways involving PKC in both yeast and mammals indicate that PKC may be a conserved regulator of cell cycle events that links signal transduction pathways and the cell-cycle machinery. In this paper, we will review current data on the cell cycle components that are targets for PKC regulation. PKC enzymes appear to operate as regulators of the cell cycle at two sites, during G1 progression and G2/M transition. In G1, the overall effect of PKC activation is **inhibition** of the cell cycle at mid to late G1. This cell cycle **inhibition** correlates with a blockage in the normal phosphorylation of the tumor suppressor retinoblastoma Rb protein, presumably through an indirect mechanism. The reduced activity of the cyclin-dependent kinase, Cdk2, appears to be the major effect of PKC activation in various cell systems. This may also underlie the **inhibition** of Rb phosphorylation exhibited by PKC activation. Several mechanisms were described in different studies on the regulation of Cdk2 activity by PKC; reduced Cdk-activating kinase activity, diminished expression of the Cdk2 partners cyclins E or A, and the increased expression of the cyclin-dependent **inhibitors**, **p21**-WAF1 and p27-KIP1, which are capable of binding to cyclin/Cdk2 complexes. PKC enzymes were also shown to play a role in G2/M transition. Among the suggested mechanisms is suppression of Cdc2 activity. However, most of the published data strongly implicate PKC in lamin B phosphorylation and nuclear envelope disassembly.
1997

4/3,AB/30 (Item 17 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11111660 BIOSIS NO.: 1[redacted]99732805
Raf-induced proliferation or cell cycle arrest is determined by the level of Raf activity with arrest mediated by **p21**-Cip1.
AUTHOR: Woods Douglas; Parry David; Cherwinski Holly; Bosch Elizabeth; Lees Emma; McMahon Martin(a)
AUTHOR ADDRESS: (a)Dep. Cell Signaling, DNAX Res. Inst., 901 California Ave., Palo Alto, CA 94304**USA
JOURNAL: Molecular and Cellular Biology 17 (9):p5598-5611 **1997**
ISSN: 0270-7306
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The Raf family of protein kinases display differences in their abilities to promote the entry of quiescent NIH 3T3 cells into the S phase of the cell cycle. Although conditional activation of DELTA-A-Raf:ER promoted cell cycle progression, activation of DELTA-Raf-1:ER and DELTA-B-Raf:ER elicited a G-1 arrest that was not overcome by exogenously added growth factors. Activation of all three DELTA-Raf:ER kinases led to elevated expression of cyclin D1 and cyclin E and reduced expression of p27-Kip1. However, activation of DELTA-B-Raf:ER and DELTA-Raf-1:ER induced the expression of **p21**-Cip1, whereas activation of DELTA-A-Raf:ER did not. A catalytically potentiated form of DELTA-A-Raf:ER, generated by point mutation, strongly induced **p21**-Cip1 expression and elicited cell cycle arrest similarly to DELTA-B-Raf:ER and DELTA-Raf-1:ER. These data suggested that the strength and duration of signaling by Raf kinases might influence the biological outcome of activation of this pathway. By titration of DELTA-B-Raf:ER activity we demonstrated that low levels of Raf activity led to activation of cyclin D1-cdk4 and cyclin E-cdk2 complexes and to cell cycle progression whereas higher Raf activity elicited cell cycle arrest correlating with **p21**-Cip1 induction and **inhibition** of cyclin-cdk activity. Using green fluorescent protein-tagged forms of DELTA-ARaf-1:ER in primary mouse embryo fibroblasts (MEFs) we demonstrated that **p21**-Cip1 was induced by Raf in a p53-independent manner, leading to cell cycle arrest. By contrast, activation of Raf in **p21**-Cip1-/- MEFs led to a robust mitogenic response that was similar to that observed in response to platelet-derived growth factor. These data indicate that, depending on the level of kinase activity, Raf can elicit either cell cycle progression or cell cycle arrest in mouse fibroblasts. The ability of Raf to elicit cell cycle arrest is strongly associated with its ability to induce the expression of the cyclin-dependent kinase **inhibitor p21**-Cip1 in a manner that bears analogy to alpha-factor arrest in Saccharomyces cerevisiae. These data are consistent with a role for Raf kinases in both proliferation and differentiation of mammalian cells.

1997

4/3,AB/31 (Item 18 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11086134 BIOSIS NO.: 199799707279
Isolation and characterization of the krev-1 gene, a novel member of ras superfamily in Neurospora crassa: Involvement in sexual cycle progression.
AUTHOR: Ito S; Matsui Y; Toh-E A; Harashima T; Inoue H(a)
AUTHOR ADDRESS: (a)Lab. Genetics, Dep. Regulation Biol., Fac. Sci., Saitama Univ., Urawa 338**Japan
JOURNAL: Molecular & General Genetics 255 (4):p429-437 **1997**
ISSN: 0026-8925
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Genes belonging to the ras superfamily encode low-molecular-weight GTP/GDP-binding proteins that are highly conserved in wide variety of organisms. We used the polymerase chain reaction (PCR) to isolate a novel member of the ras superfamily from the filamentous fungus Neurospora crassa and obtained a mammalian Krev-1 homolog. We named the gene krev-1 and analyzed its structure and function. The krev-1 gene encodes a polypeptide of 225 amino acids, which is nearly 60% homologous to the mammalian Krev-1 **p21**. The krev-1 gene product (KREV1) is functionally analogous to mammalian Krev-1 **p21** and Rsr1p/Bud1p, a Krev-1 homolog from the yeast Saccharomyces cerevisiae. GAL1-driven expression of KREV1 in a wild-type yeast strain resulted in a random budding pattern, as did its mammalian counterpart Krev-1 **p21** . We disrupted the krev-1 gene by RIP (repeat-induced point mutation), but the krev-1 disruptants showed no abnormalities. By in vitro mutagenesis, we constructed several mutant krev-1 genes (G21V, A68T, and D128A) which mimic constitutively active mutants of Ha-ras, and the krev-1 (K25N) mutant which is analogous to a dominant-negative mutant of Ha-ras. Each mutant gene was introduced into the wild-type strain and the phenotypes were analyzed. We could not observe any difference in vegetative growth between these transformants. When each strain was used as the female in mating tests, the development of perithecia from protoperithecia was **inhibited** in all cases. The results indicate that the krev-1 gene may be involved in sexual cycle progression.

1997

4/3,AB/32 (Item 19 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10973796 BIOSIS NO.: 199799594941
Homologous regions of Fen1 and **p21**-Cip1 compete for binding to the same site on PCNA: A potential mechanism to co-ordinate DNA replication and repair.
AUTHOR: Warbrick Emma; Lane David P(a); Glover David M; Cox Lynne S
AUTHOR ADDRESS: (a)CRC Lab., Dep. Biochem., Univ. Dundee, Dundee DD1 4HN** UK
JOURNAL: Oncogene 14 (19):p2313-2321 **1997**
ISSN: 0950-9232
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Following genomic damage, the cessation of DNA replication is coordinated with onset of DNA repair; this co-ordination is essential to avoid mutation and genomic instability. To investigate these phenomena, we have analysed proteins that interact with PCNA, which is required for both DNA replication and repair. One such protein is **p21**-Cip1, which **inhibits** DNA replication through its interaction with PCNA, while allowing repair to continue. We have identified an interaction between PCNA and the structure specific nuclease, Fen1, which is involved in DNA replication. Deletion analysis suggests that **p21**-Cip1 and Fen1 bind to the same region of PCNA. Within Fen1 and its homologues a small region (10 amino acids) is sufficient for PCNA binding, which contains an 8 amino acid conserved PCNA-binding motif. This motif shares critical residues with the PCNA-binding region of **p21**-Cip1. A PCNA binding peptide from **p21**-Cip1 competes with Fen1 peptides for binding to PCNA, disrupts the Fen1-PCNA complex in replicating cell extracts, and concomitantly **inhibits** DNA synthesis. Competition between homologous regions of Fen1 and **p21**-Cip1 for binding to the same site on PCNA may provide a mechanism to co-ordinate the functions of PCNA in DNA replication and repair.

1997

4/3,AB/33 (Item 20 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10788444 BIOSIS NO.: 199799409589
The influence of the proliferating cell nuclear antigen-interacting domain of **p21**-CIP1 on DNA synthesis catalyzed by the human and Saccharomyces cerevisiae polymerase delta holoenzymes.
AUTHOR: Gibbs Emma(a); Kelmans Zvi; Gulbis Jacqueline M; O'Donnell Mike; Kuriyhan John; Burgers Peter M J; Hurwitz Jerard(a)
AUTHOR ADDRESS: (a)Grad. Program Mol. Biol., Memorial Sloan-Kettering Cancer Cent., New York, NY**USA
JOURNAL: Journal of Biological Chemistry 272 (4):p2373-2381 **1997**
ISSN: 0021-9258
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In eukaryotes, processive DNA synthesis catalyzed by DNA polymerases delta and epsilon (pol delta and epsilon) requires the proliferating cell nuclear antigen (PCNA). It has recently been shown that in humans (h), the PCNA function, required for both DNA replication and nucleotide excision repair, can be inactivated by **p21**-CIP1 due to a specific interaction between hPCNA and the carboxyl terminus of **p21**-CIP1. In this report, we show that Saccharomyces cerevisiae (S. cerevisiae) PCNA-dependent pot delta-catalyzed DNA synthesis was **inhibited** less efficiently than the human system by the intact **p21**-CIP1 protein and was unaffected by the **p21**-CIP1 carboxyl-terminal peptide (codons 139-160). This species-specific response of PCNA to **p21**-CIP1-mediated **inhibition** of DNA synthesis results from a marked difference in the ability of h and S. cerevisiae PCNA to interact with **p21**-CIP1. As shown by binding studies using the surface plasmon resonance technique, hPCNA binds both full-length **p21**-CIP1 and the **p21**-CIP1 peptide-(139-160) stoichiometrically with a similar affinity (K-D apprx 2.5 nM) while S. cerevisiae PCNA binds **p21**-CIP1 with apprx 10-fold less affinity and does not interact with the **p21**-CIP1 peptide-(139-160).

1997

4/3,AB/34 (Item 21 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10669408 BIOSIS NO.: 199799290553
P202, an interferon-inducible modulator of transcription, **inhibits** transcriptional activation by the p53 tumor suppressor protein, and a segment from the p53-binding protein 1 that binds to p202 overcomes this **inhibition**.
AUTHOR: Datta Bansidhar; Li Bin; Choubey Divaker; Nallur Girish; Lengyel Peter(a)
AUTHOR ADDRESS: (a)Dep. Molecular Biophysics Biochemistry, Yale Univ., P.O. Box 208024, 333 Cedar St., New Haven, C**USA
JOURNAL: Journal of Biological Chemistry 271 (44):p27544-27555 **1996**
ISSN: 0021-9258
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: p202, an interferon-inducible murine protein, is a member of the "200 family" of proteins and is primarily nuclear. p202 is a modulator of transcription; it binds several transcription factors, including NF-kappa-B p50 and p65, AP-1 c-Fos and c-Jun, and E2F1, and **inhibits** their transcriptional activity. p202 also binds pRb, the

retinoblastoma protein and if overexpressed it retards cell proliferation. Here we report that using the yeast two-hybrid assay we found that p202 bound the murine homolog of the human p53-binding protein 1 (53BP1), a protein shown to interact with the DNA binding domain of the p53 tumor suppressor protein. p202 bound a 98-amino acid segment from 53BP1. This binding was **inhibited** by the replacement in p202 of a histidine (from the M(F/L)HATVA(T/S) sequence that is conserved among all of the 200 family proteins) by phenylalanine. We also report that overexpression of p202 **inhibited** the p53-dependent expression of reporter genes containing p53-activable segments from the mdm2 and **p21** genes, whereas a decrease in the p202 level (in consequence of the expression of 202 antisense RNA) resulted in an increase in the p53-dependent expression of these reporters. Expression of the 53BP1 segment binding to p202 overcame the **inhibition** by overexpressed p202 of the transcription of reporters mediated by the p53 or the A-P-1 transcription factors and of the proliferation of yeast.

1996

4/3,AB/35 (Item 22 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10625744 BIOSIS NO.: 199699246889
Requirement for PCNA in DNA mismatch repair at a step preceding DNA resynthesis.
AUTHOR: Umar Asad(a); Buermeyer Andrew B; Simon Jeffrey A; Thomas David C; Clark Alan B; Liskay R Michael; Kunkel Thomas A(a)
AUTHOR ADDRESS: (a)Lab. Molecular Genetics, Natl. Inst. Environ. Health Sci., Research Triangle Park, NC 27709**USA
JOURNAL: Cell 87 (1):p65-73 **1996**
ISSN: 0092-8674
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A two-hybrid system was used to screen yeast and human expression libraries for proteins that interact with mismatch repair proteins. PCNA was recovered from both libraries and shown in the case of yeast to interact with both MLH1 and MSH2. A yeast strain containing a mutation in the PCNA gene had a strongly elevated mutation rate in a dinucleotide repeat, and the rate was not further elevated in a strain also containing a mutation in MLH1. Mismatch repair activity was examined in human cell extracts using an assay that does not require DNA repair synthesis. Activity was **inhibited** by p21WAF1 or a **p21** peptide, both of which bind to PCNA, and activity was restored to **inhibited** reactions by addition of PCNA. The data suggest a PCNA requirement in mismatch repair at a step preceding DNA resynthesis. The ability of PCNA to bind to MLH1 and MSH2 may reflect linkage between mismatch repair and replication and may be relevant to the roles of mismatch repair proteins in other DNA transactions.

1996

4/3,AB/36 (Item 23 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10573686 BIOSIS NO.: 199699194831
Requirement of proliferating cell nuclear antigen in RAD6-dependent postreplicational DNA repair.
AUTHOR: Torres-Ramos Carlos A; Yoder Bonita L; Burgers Peter M J; Prakash Satya; Prakash Louise(a)

AUTHOR ADDRESS: (a)Sealy [redacted]t. Mol. Sci., Univ. Tex. Med. [redacted]nch, 6.104 Med. Res. Building, Ga[redacted]ton, TX 77555-106**USA
JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 93 (18):p9676-9681 **1996**
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The proliferating cell nuclear antigen (PCNA) acts as a processivity factor for replicative DNA polymerases and is essential for DNA replication. In vitro studies have suggested a role for PCNA in the repair synthesis step of nucleotide excision repair, and PCNA interacts with the cyclin-dependent kinase **inhibitor p21**. However, because of the lack of genetic evidence, it is not clear which of the DNA repair processes are in fact affected by PCNA in vivo. Here, we describe a PCNA mutation, pol30-46, that confers ultraviolet (UV) sensitivity but has no effect on growth or cell cycle progression, and the mutant pcna interacts normally with DNA polymerase delta and epsilon. Genetic studies indicate that the pol30-46 mutation is specifically defective in RAD6-dependent postreplicational repair of UV damaged DNA, and this mutation impairs the error-free mode of bypass repair. These results implicate a role for PCNA as an intermediary between DNA replication and postreplicational DNA repair.

1996

4/3,AB/37 (Item 24 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10566791 BIOSIS NO.: 199699187936
Novel anti-carcinogenic activity of an organosulfide from garlic: **Inhibition** of H-ras oncogene transformed tumor growth in vivo by diallyl disulfide is associated with **inhibition** of **p21**-H-ras processing.
AUTHOR: Singh Shivendra V(a); Moham Rajiv R; Agarwal Rajesh; Benson Patrick J; He Xun; Rudy Maura A; Xia Hong; Katoh Arthur; Srivastava Sanjay K; Mukhtar Hasan; Gupta Vicram; Zaren Howard A
AUTHOR ADDRESS: (a)Cancer Res. Lab., Mercy Cancer Inst., Mercy Hosp. Pittsburgh, Pittsburgh, PA 15219**USA
JOURNAL: Biochemical and Biophysical Research Communications 225 (2):p 660-665 **1996**
ISSN: 0006-291X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In this study, we report a novel anticarcinogenic activity of an organosulfur compound from garlic, diallyl disulfide (DADS). DADS treatment significantly **inhibited** the growth of H-ras oncogene transformed tumors in nude mice. As compared to controls, the appearance of tumors was also delayed markedly by oral administration of DADS. The **inhibition** of tumor growth by DADS treatment correlated with the **inhibition** of **p21**-H-ras membrane association in the tumor tissue. The levels of membrane associated **p21**-H-ras were markedly lower in the tumor tissues of DADS treated mice as compared to controls. An opposite trend, however, was evident for cytosolic **p21**-H-ras. Furthermore, DADS treatment resulted in a significant **inhibition** of hepatic as well as tumoral 3-hydroxy-3-methylglutaryl coenzyme A reductase activity. These results indicate that DADS suppresses the growth of H-ras oncogene transformed tumors in nude mice by **inhibiting** the membrane association of tumoral **p21**-H-ras.

1996

4/3,AB/38 (Item 25 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10368950 BIOSIS NO.: 199698823868
Heterologous expression of the human cyclin-dependent kinase **inhibitor p21**-Cip1 in the fission yeast, Schizosaccharomyces pombe reveals a role for PCNA in the chk1+ cell cycle checkpoint pathway.
AUTHOR: Tournier Sylvie; Leroy Dorothee; Goubin Francoise; Ducommun Bernard ; Hyams Jeremy S(a)
AUTHOR ADDRESS: (a)Dep. Biol., Univ. Coll. London, London WC1E 6BT**UK
JOURNAL: Molecular Biology of the Cell 7 (4):p651-662 **1996**
ISSN: 1059-1524
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Fission yeast cells expressing the human gene encoding the cyclin-dependent kinase **inhibitor** protein **p21**-Cip1 were severely compromised for cell cycle progress. The degree of cell cycle **inhibition** was related to the level of **p21**-Cip1 expression. **Inhibited** cells had a 2C DNA content and were judged by cytology and pulsed field gel electrophoresis to be in the G2 phase of the cell cycle. **p21**-Cip1 accumulated in the nucleus and was fission essayed as in mammalian cells. Elimination of p34-cdlc-2 binding by mutation within associated with p34-cdc2 and PCNA. Thus, **p21**-Cip1 interacts with the same targets in the cyclin-dependent kinase binding domain of **p21**-Cip1 exaggerated the cell cycle delay phenotype. By contrast, elimination of PCNA binding by mutation within the PCNA-binding domain completely abolished the cell cycle **inhibitory** effects. Yeast cells expressing wild-type **p21**-Cip1 and the mutant form that is unable to bind p34-cdc2 showed enhanced sensitivity to UV. Cell cycle **inhibition** by **p21**-Cip1 was largely abolished by deletion of the chk1+ gene that monitors radiation damage and was considerably enhanced in cells deleted for the rad3+ gene that monitors both DNA damage and the completion of DNA synthesis. Overexpression of PCNA also resulted in cell cycle arrest in G2 and this phenotype was also abolished by deletion of chk1+ and enhanced in cells deleted for rad3+. These results formally establish a link between PCNA and the products of the rad3+ and chk1+ checkpoint genes.

1996

4/3,AB/39 (Item 26 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10363971 BIOSIS NO.: 199698818889
Human and **plant** proliferating-cell nuclear antigen have a highly conserved binding site for the p53-inducible gene product **p21**-WAF1.
AUTHOR: Ball Kathryn L(a); Lane David P
AUTHOR ADDRESS: (a)CRC Cell Transformation Group, Dep. Biochem., Med. Sci. Inst., Univ. Dundee, Dundee DD1 4HN**UK
JOURNAL: European Journal of Biochemistry 237 (3):p854-861 **1996**
ISSN: 0014-2956
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The mechanisms whereby higher **plants** respond to environmental agents that damage their DNA, which leads to the arrest of

cell division, is poorly understood. In mammalian cells the tumour-suppressor protein p53 plays a central role in a DNA-damage-induced cell-cycle-checkpoint pathway by induction of transcription of a set of gene products that have a direct role in a DNA-damage-induced cell-cycle growth arrest. One such protein, **p21**-WAF1, has been shown to be essential for radiation-induced growth arrest. There appear to be at least two cellular targets of **p21**-WAF1 during checkpoint control, the G-1-cyclin-dependent kinases (CDK) and proliferating-cell nuclear antigen (PCNA). The aim of the research reported here was to determine whether the interactions between the human growth **inhibitor p21**-WAF1 and PCNA from **plants** and humans are conserved. If so, this would suggest that modulation of PCNA activity may play an important role in **plant** responses. to DNA damage and would imply that functional homologue(s) of **p21**-WAF1 exist in **plants**. We show that the **p21**-WAF1-interaction domain of PCNA is conserved between humans and **plants**. A peptide that contains the site of human **p21**-WAF1 that binds human PCNA has been used to precipitate PCNA from crude pea (Pisum savitum) extracts. We used the **p21**-WAF1 peptide as an affinity matrix and showed that pea PCNA bound in a specific high-affinity manner. This finding was used to develop a purification protocol that allowed PCNA from **plant** tissue to be purified to homogeneity. Pure pea PCNA forms a stable complex with full-length human **p21**-WAF1 and the specific amino acids of **p21**-WAF1 required for the interaction have been identified. The critical residues were identical to those required for binding to human PCNA, which indicates that the interaction of human **p21**-WAF1 with PCNA is highly conserved at each amino acid position between pea and human.

1996

4/3,AB/40 (Item 27 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10271334 BIOSIS NO.: 199698726252
The **p21**-RAS farnesyltransferase alpha subunit in TGF-beta and activin signaling.
AUTHOR: Wang Tongwen(a); Danielson Paul D; Li Bi-Yu; Shah Paresh C; Kim Stephen D; Donahoe Patricia K(a)
AUTHOR ADDRESS: (a)Pediatric Surgical Res. Lab., Massachusetts Gen. Hosp., Boston, MA 02114**USA
JOURNAL: Science (Washington D C) 271 (5252):p1120-1122 **1996**
ISSN: 0036-8075
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The alpha subunit of **p21**-RAS farnesyltransferase (FNTA), which is also shared by geranylgeranyltransferase, was isolated as a specific cytoplasmic interactor of the transforming growth factor-beta (TGF-beta) and activin type I receptors with the use of the yeast two-hybrid system. FNTA interacts specifically with ligand-free TGF-beta type I receptor but is phosphorylated and released upon ligand binding. Furthermore, the release is dependent on the kinase activity of the TGF-beta type II receptor. Thus, the growth **inhibitory** and differentiative pathways activated by TGF-beta and activin involve novel mechanisms of serine-threonine receptor phosphorylation-dependent release of cytoplasmic interactors and regulation of the activation of small G proteins, such as **p21**-RAS.

1996

4/3,AB/41 (Item 28 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)
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10184638 BIOSIS NO.: 199698639556
Fission yeast pak1+ encodes a protein kinase that interacts with Cdc42p and is involved in the control of cell polarity and mating.
AUTHOR: Ottilie Sabine; Miller Peter J; Johnson Douglas I; Creasy Caretha L ; Sells Mary Ann; Bagrodia Shubha; Forsburg Susan L; Chernoff Jonathan(a)
AUTHOR ADDRESS: (a)Fox Chase Cancer Cent., 7701 Burholme Avenue, Philadelphia, PA 19111**USA
JOURNAL: EMBO (European Molecular Biology Organization) Journal 14 (23):p 5908-5919 **1995**
ISSN: 0261-4189
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A STE20/p65-pak homolog was isolated from fission yeast by PCR. The pak1+ gene encodes a 72 kDa protein containing a putative **p21** -binding domain near its amino-terminus and a serine/threonine kinase domain near its carboxyl-terminus. The Pak1-protein autophosphorylates on serine residues and preferentially binds to activated Cdc42p both in vitro and in vivo. This binding is mediated through the **p21** binding domain on Pak1p and the effector domain on Cdc42p. Overexpression of an inactive mutant form of pak1 gives rise to cells with markedly abnormal shape with mislocalized actin staining. Pak1 overexpression does not, however, suppress lethality associated with cdc42-null cells or the morphologic defect caused by overexpression of mutant cdc42 alleles. Gene disruption of pak1+ establishes that, like cdc42+, pa1+ function is required for cell viability. In budding yeast, pak1 expression restores mating function to STE20-null cells and, in fission yeast, overexpression of an inactive form of Pak **inhibits** mating. These results indicate that the Pak1 protein is likely to be an effector for Cdc42p or a related GTPase, and suggest that Pak1p is involved in the maintenance of cell polarity and in mating.

1995

4/3,AB/42 (Item 29 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10172623 BIOSIS NO.: 199698627541
Properties and regulation of the catalytic domain of Ira2P, a Saccharomyces cerevisiae GTPase-activating protein of Ras2P.
AUTHOR: Parrini Maria Carla; Jacquet Eric; Bernardi Alberto; Jacquet Michel ; Parmeggiani Andrea(a)
AUTHOR ADDRESS: (a)Groupe Biophysique, Ecole Polytechnique, F-91128 Palaiseau Cedex**France
JOURNAL: Biochemistry 34 (42):p13776-13783 **1995**
ISSN: 0006-2960
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: This work describes the biochemical characterization of the catalytic domain of Ira2p, a Saccharomyces cerevisiae GTPase-activating protein (GAP) regulating the RAS gene products. A fragment of 383 residues (amino acids 1644-2026) was produced in Escherichia coli as glutathione S-transferase fusion protein (GST-Ira2p-383) and highly purified (gt 90%) by affinity chromatography. The affinity of Ras2p for the GST-fused Ira2p-383 was 18 mu-M and the maximal stimulation of the Ras2p GTPase activity 6 000 times. The Ira2p activity was confirmed to be strictly specific for Ras2p, no stimulatory effect on human c-H-ras

p21 GTPase being detectable. Comparison with the GAP-like domain of mammalian p120-GAP and neurofibromin using yeast Ras2p as substrate showed that Ira2p-383 has an affinity and turnover intermediary between GAP-334 and NF1-414. The activity of Ira2p-383 was strongly **inhibited** by monovalent and divalent salts. The simultaneous presence of the catalytic domains of Ira2p and the yeast GDP/GTP exchange factor Cdc25p induced on Ras2p a multiple-round reaction of GTP hydrolysis and GDP/GTP exchange, showing that it is possible to reconstitute in vitro a S. cerevisiae system suitable for the study of the regulation of the Ras2p GDP/GTP cycle. The tubulin partially **inhibited** (25%) the GAP activity of the Ira2p-383. A larger Ira2p catalytic fragment, Ira2p-505 (amino acids 1549-2053), that showed the same Km for Ras2p as Ira2p-383, was also **inhibited** by tubulin to the same extent but with a higher affinity than Irap-383. This indicates that the conserved catalytic domain contains a binding site for tubulin that is extended to its N-terminal flanking region. These results show that the **inhibition** of neurofibromin by tubulin (Bollag, G., McCormick. F., & Clark, R. (1993) EMBO J. 12, 1923-1927) is a property shared with Ira2p.

1995

4/3,AB/43 (Item 30 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10133842 BIOSIS NO.: 199698588760
Gadd45 is a nuclear cell cycle regulated protein which interacts with **p21**-Cip1.
AUTHOR: Kearsey Jonathan M; Coates Philip J; Prescott Alan R; Warbrick Emma ; Hall Peter A(a)
AUTHOR ADDRESS: (a)Dep. Pathol., Univ. Dundee, Dundee, Scotland DD1 9SY**UK
JOURNAL: Oncogene 11 (9):p1675-1683 **1995**
ISSN: 0950-9232
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: GADD45 was originally identified as a cDNA clone induced by growth arrest and DNA damage. We show that Gadd45 is a nuclear protein, widely expressed in normal tissues, particularly in quiescent cellular populations. Using cell synchronisation methods we show that Gadd45 levels are highest in the G1 phase of the cell cycle, and are greatly reduced during S phase. Immunoprecipitation of Gadd45 from mammalian cells reveals that it is tightly associated with a protein which reacts with antibodies to the cyclin dependent kinase **inhibitor p21** -Cip1. Binding of recombinant Gadd45 protein to overlapping **p21** -Cip1 peptides in ELISA assays and use of the yeast two hybrid assay show that Gadd45 directly interacts with this cell cycle **inhibitor**. These data suggest that Gadd45 may act in the regulation of the cell cycle. It is postulated that the interactions of Gadd45 with both **p21**-Cip1 and PCNA are important for the modulation of cell cycles, and for the **inhibition** of DNA replication.

1995

4/3,AB/44 (Item 31 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09829157 BIOSIS NO.: 199598284075
A small peptide **inhibitor** of DNA replication defines the site of interaction between the cyclin-dependent kinase **inhibitor p21**

-WAF1 and proliferating [redacted]ll nuclear antigen.
AUTHOR: Warbrick Emma(a); [redacted]e David P; Glover David M; Co[redacted]nne S
AUTHOR ADDRESS: (a)Cancer Res. Campaign Lab., Dep. Anat. Physiol., Univ. Dundee, Dundee DD1 4HN**UK
JOURNAL: Current Biology 5 (3):p275-282 **1995**
ISSN: 0960-9822
DOCUMENT TYPE: Article
RECORD TYPE: Citation
LANGUAGE: English
1995

4/3,AB/45 (Item 32 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09731632 BIOSIS NO.: 199598186550
Properties of the catalytic domain of Sdc25p, a yeast GDP/GTP exchange factor of Ras proteins: Complexation with wild-type Ras2p, (S24N)Ras2p and (R80D, N81D)Ras2p.
AUTHOR: Poullet Patrick; Crechet Jean-Bernard; Bernardi Alberto; Parmeggiani Andrea(a)
AUTHOR ADDRESS: (a)Structure Diverse Interventions no. 61840 du Centre Natl. Recherche Sci., Lab. Biochimie, Ecole **France
JOURNAL: European Journal of Biochemistry 227 (1-2):p537-544 **1995**
ISSN: 0014-2956
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The catalytic domain of the Saccharomyces cerevisiae SDC25 gene product, including the last 550 C-terminal residues (Sdc25p-C), was produced as an Escherichia coli recombinant protein fused with glutathione S-transferase. The highly purified (greater than 95 %) stable fusion protein, obtained by affinity chromatography, was very active in enhancing the dissociation rate or the GDP/GTP exchange of the GDP complex of Ras2p or human H-ras **p21**. This activity was further increased (three times) by glutathione S-transferase cleavage with thrombin. The stimulation of the guanine nucleotide release by Sdc25p-C was stronger for Ras2p cntdot GDP than Ras2p cntdot GTP, an effect that was less pronounced in the case of the **p21** complexes. The association rate of the Ras2p cntdot GDP (GTP) complex was also enhanced by Sdc25p-C. Monovalent and divalent salts **inhibit** the nucleotide-releasing activity of Sdc25p-C. Retention phenomena occurring on gel-filtration chromatography hindered the use of highly purified Sdc25p-C to study the formation of stable complexes with Ras2p. For this purpose, Sdc25p-C was produced as a non-glutathione-S-transferase fusion protein via pTTQ19. Upon partial purification, this product yielded a 54-kDa truncated form of Sdc25p-C (truncated Sdc25p-C) showing the same specific activity as the 64-kDa Sdc25p-C protein. On gel filtration, truncated Sdc25p-C and nucleotide-free Ras2p (or **p21**) formed a stable 1:1 stoichiometric complex that was dissociated by increasing concentrations of GDP. The properties of this complex were analyzed by using the mutant (S24N)Ras2p, the homologue of (S17N)**p21** known to induce a dominant negative phenotype, (R80D, N81D)Ras2p, a recessive negative mutant insensitive to the truncated form of Sdc25p-C in vitro. The complex with (S24N)Ras2p was greater than 100-fold less sensitive to the dissociating effect of GDP, whereas (R80D, N81D)Ras2p was unable to form a stable complex with truncated Sdc25p-C. These results strongly suggest that the residues R80 and N81 are situated in or closely associated with the Ras2p specific site binding Sdc25p.

1995

4/3,AB/46 (Item 33 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09680861 BIOSIS NO.: 199598135779
Use of the cyclin E restriction point to map cell arrest in G-1 induced by n-butyrate, cycloheximide, staurosporine, lovastatin, mimosine and quercetin.
AUTHOR: Gong Jianping; Traganos Frank; Darzynkiewicz Zbigniew(a)
AUTHOR ADDRESS: (a)Cancer Res. Inst., New York Med. Coll., 100 Grasslands Rd., Elmsford, NY 10523**USA
JOURNAL: International Journal of Oncology 4 (4):p803-808 **1994**
ISSN: 1019-6439
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Cyclin E, a member of the G-1 cyclin family, is an integral component of the complex machinery of the cell cycle. This protein is synthesized late in the G-1 phase of the cycle and its transient association with p33-cdk2 is essential for cell entrance to S phase. Using bivariate DNA content cyclin E expression flow cytometric analysis, we have compared the point of action in G-1 of several agents with diverse mechanisms of action in terms of its relationship to the cyclin E restriction point: cell arrest prior to the onset of cyclin E synthesis was expected to result in accumulation of cyclin E negative cells (G-1cyE-) whereas arrest past this point was expected to result in accumulation of G-1 cells with an increased cyclin E content (G-1cyE+). Incubation of MOLT-4 cells with n-butyrate (which induces hyperacetylation of histories and hypophosphorylation of histone H1) and the protein synthesis **inhibitor** cycloheximide arrested them in G-1cyE-. Likewise, incubation of c-ras transformed bladder carcinoma T24 cells with lovastatin (presumed to interfere with isoprenylation of **p21**-ras and thus affecting the signal transduction pathway), or normal, mitogen stimulated human lymphocytes with staurosporine (a protein kinase **inhibitor**) led to cell arrest in G-1cyE-. In contrast, growth of MOLT-4 cells in the presence of the bioflavonoid quercetin or **plant** amino acid mimosine, resulted in their arrest at the G-1 point past the onset of cyclin E synthesis (G-1cyE+). Mapping the point(s) of action of drugs that perturb progression in the cycle with respect to the onset of synthesis of cyclin proteins offers some advantages compared to temporal mapping; the latter may vary due to intrinsic differences between cell types in the duration of G-1, the induction of unbalanced growth, etc.

1994

4/3,AB/47 (Item 34 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09547576 BIOSIS NO.: 199598002494
RalGDS Family Members Interact with the Effector Loop of ras **p21**.
AUTHOR: Kikuchi Akira; Demo Susan D; Ye Zhi-Hai; Chen Yen-Wen; Williams Lewis T(a)
AUTHOR ADDRESS: (a)Univ. California San Francisco, Parnassus Ave., CVRI, Box 0130, San Francisco, CA 94143-0130**USA
JOURNAL: Molecular and Cellular Biology 14 (11):p7483-7491 **1994**
ISSN: 0270-7306
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Using a yeast two-hybrid system, we identified a novel protein

which interacts with ras p21. This protein shares 69% amino acid homology with ral guanine nucleotide dissociation stimulator (ralGDS), a GDP/GTP exchange protein for ral p24. We designated this protein RGL, for ralGDS-like. Using the yeast two-hybrid system, we found that an effector loop mutant of ras **p21** was defective in interacting with the ras, **p21**-interacting domain of RGL, suggesting that this domain binds to ras **p21** through the effector loop of ras **p21**. Since ralGDS contained a region highly homologous with the ras **p21**-interacting domain of RGL, we examined whether ralGDS could interact with ras **p21**. In the yeast two-hybrid system, ralGDS failed to interact with an effector loop mutant of ras **p21**. In insect cells, ralGDS made a complex with v-ras **p21** but not with a dominant negative mutant of ras **p21**. ralGDS interacted with the GTP-bound form of ras **p21** but not with the GDP-bound form in vitro. ralGDS **inhibited** both the GTPase-activating activity of the neurofibromatosis gene product (NF1) for ras **p21** and the interaction of Raf with ras **p21** in vitro. These results demonstrate that ralGDS specifically interacts with the active form of ras **p21** and that ralGDS can compete with NF1 and Raf for binding to the effector loop of ras **p21**. Therefore, ralGDS family members may be effector proteins of ras **p21** or may **inhibit** interactions between ras **p21** and its effectors.

1994

4/3,AB/48 (Item 35 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09459984 BIOSIS NO.: 199497468354
In the budding yeast Kluyveromyces marxianus, adenylate cyclase is regulated by Ras protein(s) in vitro.
AUTHOR: Verzotti Enrico; Geymonat Marco; Valetti Francesca; Lanzetti Letizia; Giunta Carlo(a)
AUTHOR ADDRESS: (a)Dipartimento Biologia Animale, Universita Torino, Via Accademia Albertina, 17-10123 Torino**Italy
JOURNAL: Yeast 10 (8):p993-1001 **1994**
ISSN: 0749-503X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The presence of adenylate cyclase activity was first demonstrated in membrane fractions from the budding yeast Kluyveromyces marxianus. The enzyme showed a Mn-2+- and Mg-2+-dependent activity, with optimal pH at around 6 as observed in other yeast species. As in Saccharomyces cerevisiae, where adenylate cyclase is regulated by RAS1 and RAS2, we detected a guanyl nucleotide-dependent activity. Interestingly Y13-259 monoclonal antibody, raised against mammalian **p21**-Ha-ras, **inhibited** Mg-2+ plus GTP-gamma-S-dependent cAMP production, suggesting that the GTP binding proteins involved in adenylate cyclase regulation could be Ras proteins. The same antibody recognized on Western blot and immunoprecipitated a 40 kDa polypeptide from K. marxianus crude membranes. This polypeptide was not detected by an anti-RAS2 polyclonal antibody raised against S. cerevisiae RAS2 protein, suggesting that Ras proteins from the two species could be structurally different.

1994

4/3,AB/49 (Item 36 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09037148 BIOSIS NO.: 199497045518

Inhibition of SDC25 C-domain-induced guanine-nucleotide exchange by guanine ring binding domain mutants of v-H-ras.
AUTHOR: Hwang Yu-Wen(a); Zhong Jie-Ming; Poullet Patrick; Parmeggiani Andrea
AUTHOR ADDRESS: (a)Mol. Biol. Dep., New York State Inst. Basic Res. Developmental Disabilities, 1050 Forest Hill Rd**USA
JOURNAL: Journal of Biological Chemistry 268 (33):p24692-24698 **1993**
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Guanine-nucleotide exchange is the reaction that controls the activation of H-ras **p21**. This reaction is stimulated by the guanine-nucleotide exchange factor. In this study we show that H-ras **p21** harboring guanine ring binding domain (the conserved NKXD motif) mutations, such as N116I or K117E, are potent **inhibitors** of H-ras **p21** guanine-nucleotide exchange reaction promoted by SDC25C (Saccharomyces cerevisiae SDC25 C-domain gene product), a guanine-nucleotide exchange factor. The **inhibition** is due to the formation of a stable but catalytically inactive complex consisting of the H-ras mutant and SDC25C. By examining the interaction of v-H-ras(N116I) or v-H-ras(K117E) with SDC25C at different concentrations of guanine-nucleotide, we demonstrate that the mechanism of SDC25C-promoted guanine-nucleotide exchange proceeds through the following pathway. First, SDC25C binds to H-ras and forms an intermediate H-ras cntdot SDC25C complex; subsequently, an incoming guanine-nucleotide dissociates the complex, releasing SDC25C from H-ras and causes guanine-nucleotide exchange. This mechanism is similar to the one proposed for Escherichia coli elongation factor Ts-catalyzed guanine-nucleotide exchange.

1993

4/3,AB/50 (Item 37 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08935964 BIOSIS NO.: 199396087465
Normal and oncogenic **p21**-ras proteins bind to the amino-terminal regulatory domain of c-raf-1.
AUTHOR: Zhang Xian-Feng; Settleman Jeffrey; Kyriakis John M; Takeuchi-Suzuki Erika; Elledge Stephen J; Marshall Mark S; Bruder Joseph T; Rapp Ulf R; Avruch Joseph(a)
AUTHOR ADDRESS: (a)Diabetes Unit Med. Serv., Dep. Med., Harvard Med. Sch., Massachusetts General Hosp. East, 149 13**USA
JOURNAL: Nature (London) 364 (6435):p308-313 **1993**
ISSN: 0028-0836
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In higher eukaryotes, the Ras and Raf-1 proto-oncoproteins transduce growth and differentiation signals initiated by tyrosine kinases. The Ras polypeptide and the amino-terminal regulatory domain of Raf-1(residues 1-257) are shown to interact, directly in vitro and in a yeast expression system. Raf-1(1-257) binds GTP-Ras in preference to GDP-Ras, and **inhibits** Ras-GAP activity. Mutations in and around the Ras effector domain impair Ras binding to Ras-1(1-257) and Ras transforming activity in parallel.

1993

4/3,AB/51 (Item 38 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08890279 BIOSIS NO.: 199396041780
A novel functional target for tumor-promoting phorbol esters and lysophosphatidic acid: The p21rac-GTPase activating protein n-chimaerin.
AUTHOR: Ahmed Sohail(a); Lee Joel; Kozman Robert; Best Anthony; Monfries Clinton; Lim Louis
AUTHOR ADDRESS: (a)Dep. Neurochemistry, Inst. Neurol., 1 Wakefield St., London WC1N 1PJ**UK
JOURNAL: Journal of Biological Chemistry 268 (15):p10709-10712 **1993**
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Phorbol esters are potent tumor promoters widely used for investigating mechanisms of cell transformation with protein kinase C (PKC) generally considered as being their only protein target. Lysophosphatidic acid (LPA) can act as a mitogen, affecting cell shape and the actin cytoskeleton. There is no identified functional target for LPA. We have isolated a cDNA encoding a protein n-chimaerin that is a high affinity phorbol ester receptor and a **p21** rac-GTPase activating protein (rac-GAP). **p21** rac is a member of the ras superfamily of small molecular weight GTP-binding proteins, which stimulates actin microfilament formation in Swiss 3T3 cells and superoxide production by the neutrophil oxidase. We now show that the rac-GAP activity of n-chimaerin is stimulated by phosphatidylserine (PS) and phosphatidic acid (PA) and that phorbol esters can synergize with PS and PA. LPA, in contrast, was found to **inhibit** n-chimaerin. The phospholipid/phorbol ester modulation of the rac-GAP activity requires the PKC-like cysteine-rich domain of n-chimaerin. Thus, n-chimaerin is a novel functional target (distinct from PKC) for both phorbol esters and LPA. These data suggest that the physiological role of n-chimaerin is to link events initiating at the cell surface/membrane with p21rac effector pathways.

1993

4/3,AB/52 (Item 39 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08333358 BIOSIS NO.: 000094084606
MOLECULAR CLONING OF CDNAS ENCODING A GUANINE-NUCLEOTIDE-RELEASING FACTOR FOR RAS **P21**
AUTHOR: SHOU C; FARNSWORTH C L; NEEL B G; FEIG L A
AUTHOR ADDRESS: DEP. BIOCHEM., TUFTS UNIV. SCH. MED., BOSTON, MASS. 02111.
JOURNAL: NATURE (LOND) 358 (6384). 1992. 351-354. **1992**
FULL JOURNAL NAME: NATURE (London)
CODEN: NATUA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The stimulation of a variety of cell surface receptors promotes the accumulation of the active, GTP-bound form of Ras proteins in cells. This is a critical step in signal transduction because **inhibition** of Ras activation by anti-Ras antibodies or dominant **inhibitory** Ras mutants blocks many of the effects of these receptors on cellular function. To reach the active GTP-bound state, Ras proteins must first release bound GDP. This rate-limiting step in GTP binding is thought to be catalysed by a guanine-nucleotide-releasing factor (GRF). Here we report the cloning of complementary DNAs from rat brain library that

encode a .apprx. 140K GR[redacted] for Ras **p21** (p140Ras-GRF). Its carboxy-terminal region[redacted] similar to that of CDC25, a GE[redacted] for Saccharomyces cerevisiae RAS. This portion of RAS-GRF accelerated the release of GDP from RasH and RasN **p21** in vitro, but not from the related RAlA, or CDC42Hs GTP-binding proteins. A region in the amino-terminal end of the Ras-GRF is similar to both the human break point cluster protein, Bcr, and the dbl oncogene product, a guanine-nucleotide-releasing factor for CDC42Hs. An understanding of Ras-GRF function will enhance our knowledge of the many signal transduction pathways mediated by RAS proteins.

1992

4/3,AB/53 (Item 40 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07772336 BIOSIS NO.: 000092075707
RESOLUTION OF A LOW MOLECULAR WEIGHT G PROTEIN IN NEUTROPHIL CYTOSOL REQUIRED FOR NADPH OXIDASE ACTIVATION AND RECONSTITUTION BY RECOMBINANT KREV-1 PROTEIN
AUTHOR: EKLUND E; MARSHALL M; GIBBS J B; CREAN C D; GABIG T G
AUTHOR ADDRESS: DIV. HEMATOL./ONCOL., MED. RES. LIBRARY BUILDING, ROOM 442, 975 W. WALNUT ST., INDIANAPOLIS, INDIANA 46202.
JOURNAL: J BIOL CHEM 266 (21). 1991. 13964-13970. **1991**
FULL JOURNAL NAME: Journal of Biological Chemistry
CODEN: JBCHA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Activation of the membrane associated NADPH oxidase in intact human neutrophils requires a receptor-associated heterotrimeric GTP-binding protein that is sensitive to pertussis toxin. Activation of this NADPH oxidase by arachidonate in a cell-free system requires an additional downstream pertussis toxin-insensitive G protein (Gabig, T.G., English, D., Akard, L. P., and Schell, M.J. (1987) (J. Biol. Chem. 262, 1685-1690) that is located in the cytosolic fraction of unstimulated cells (Gabig, T. G., Eklund, E. A., Potter, G. B., and Dykes, J. R. (1990) J. Immunol. 145, 945-951). In the present study, immunodepletion of G proteins from the cytosolic fraction of unstimulated neutrophils resulted in a loss of the ability to activate NADPH oxidase in the membrane fraction. The activity in immunodepleted cytosol was fully reconstituted by a pratially purified fraction from neutrophil cytosol and contained a 21-kDa GTP-binding protein. Purified human recombinant Krev-1 **p21** also completely reconstituted immunodepleted cytosol whereas recombinant human H-ras **p21** or yeast RAS GTP-binding proteins had no reconstitutive activity. Rabbit antisera raised against a synthetic peptide corresponding to the effector region of Krev-1 (amino acids 31-43) completely **inhibited** cell-free NADPH oxidase activation, and this **inhibition** was blocked by the synthetic 31-43 peptide. An **inhibitory** monoclonal antibody specific for ras **p21** amino acids 60-77 (Y13-259) had no effect on cell-free NADPH oxidase activation. Activation of the NADPH oxidase in intact neutrophils by stimulation with phorbol myristate acetate caused a marked increase in the amount of membrane-associated antigen recognized by 151 antiserum on Western blot. Thus a G protein in the cytosol of unstimulated neutrophils antigenically and functionally related to Krev-1 may be the downstream effector G protein for NADPH oxidase activation. This system represents a unique model to study molecular interactions of a ras-like G protein.
1991

4/3,AB/54 (Item 41 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07306579 BIOSIS NO.: 000090086468
MOLECULAR CLONING AND CHARACTERIZATION OF A NOVEL TYPE OF REGULATORY PROTEIN GDI FOR SMG P25A A RAS **P21**-LIKE GTP-BINDING PROTEIN
AUTHOR: MATSUI Y; KIKUCHI A; ARAKI S; HATA Y; KONDO J; TERANISHI Y; TAKAI Y
AUTHOR ADDRESS: DEP. BIOCHEM., KOBE UNIV. SCH. MED., KOBE 650, JPN.
JOURNAL: MOL CELL BIOL 10 (8). 1990. 4116-4122. **1990**
FULL JOURNAL NAME: Molecular and Cellular Biology
CODEN: MCEBD
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: We recently purified to near homogeneity a novel type of regulatory protein for smg p25A, a ras **p21**-like GTP-binding protein, from bovine brain cytosol. This regulatory protein, named smg p25A GDP dissociation **inhibition** (GDI), regulates the GDP-GTP exchange reaction of smg p25A by **inhibiting** dissociation of GDP from and subsequent binding of GTP to it. In the present studies, we isolated and sequenced the cDNA of smg p25A GDI from a bovine brain cDNA library by using an oligonucleotide probe designed from the partial amino acid sequence of purified smg p25A GDI. The cDNA has an open reading frame that encodes a protein of 447 amino acids with a calculated Mr of 50,565. This Mr is similar to those of the purified smg p25A GDI estimated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and source density gradient ultracentrifugation, which are about 54,000 and 65,000, respectively. The isolated cDNA is expressed in Escherichi coli, and the encoded protein exhibits GDI activity, smg p25A GDI is hydrophilic overall, except for one hydrophobic region near the N terminus. smg p25A GDI shares low amino acid sequence homologoy with the Saccharomyces cerevisiae CDC25-encoded protein, which has been suggested to serve as a factor that regulates the GDP-GTP exchange reaction of the yeast RAS2-encoded protein, but not with the .beta..gamma. subunits of GTP-binding proteins having an .alpha..beta..gamma. subunit structure, such as Gs and Gi. The smg p25A GDI mRNA was present in various tissues, including not only tissues in which smg p25A was detectable but also tissues in which it was not detectable. This fact has raised the possibility that smg p25A GDI interacts with another G protein in tissues in which smg p25A is absent.

1990

4/3,AB/55 (Item 42 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

06970115 BIOSIS NO.: 000089081874
EVOLUTION OF PROTEINS OF THE CYSTATIN SUPERFAMILY
AUTHOR: RAWLINGS N D; BARRETT A J
AUTHOR ADDRESS: DEP. BIOCHEM., STRANGEWAYS RES. LAB., WORTS CAUSEWAY, CAMBRIDGE CB1 4RN, UK.
JOURNAL: J MOL EVOL 30 (1). 1990. 60-71. **1990**
FULL JOURNAL NAME: Journal of Molecular Evolution
CODEN: JMEVA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: We have examined the amino acid sequences of a number of proteins that have been suggested to be related to chicken cystatin, a protein from chicken egg white that **inhibits** cysteine proteinases. On the basis of statistical analysis, the following proteins were found to be members of the cystatin superfamily: human cystatin A, rat cystatin A(.alpha.), human cystatin B, rat cystatin B(.beta.), rice cystatin, human cystatin C, ox colostrum cystatin, human cystatin S, human cystatin

SA, human cystatin SN, chicken cystatin, puff adder cystatin, human kininogen, ox kininogen, rat kininogen, rat T-kininogens 1 and 2, human .alpha.2HS-glycoprotein, and human histidine-rich glycoprotein. Fibronectin is shown not to be a member of this superfamily, and the c-Ha-ras oncogene protein **p21**(Val-12) probably is not a member also. It was convenient to divide members of the superfamily into four types on the basis of the presence of one, two, or three copies of cystatin-like segments and the presence or absence of disulfide bonds. Evolutionary dendrograms were calculated by three methods, and from these we have constructed a scheme depicting the sequence of events in the evolution of these proteins. We suggest that about 1000 million years ago a precursor containing disulfide loops appeared, and that all disulfide-containing cystatins are derived from this. We follow the evolution of the proteins of the superfamily along four main lineages, with special attention to the part that duplication of segments has played in the development of the more complex molecules.

1990

4/3,AB/56 (Item 43 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

06207830 BIOSIS NO.: 000086042012
INHIBITION OF YEAST ADENYLATE CYCLASE BY ANTIBODIES TO RAS **P21**
AUTHOR: GIBBS J B; MARSICO-AHERN J D; SCOLNICK E M; SIGAL I S
AUTHOR ADDRESS: DEP. VIRUS AND CELL BIOL., MERCK, SHARP AND DOHME RES. LAB., WEST POINT, PA. 19486, USA.
JOURNAL: BIOCHEM J 252 (1). 1988. 289-292. **1988**
FULL JOURNAL NAME: Biochemical Journal
CODEN: BIJOA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Monoclonal antibody Y13-259 to ras **p21** was shown to bind to the highly conserved residues in the region 63-73 and to neutralize ras action in the Saccharomyces cerevisiae adenylate cyclase system. **Inhibition** of adenylate cyclase activity in isolated membranes by antibody Y13-259 occurred after a lag period of 6 min. This lag corresponded to the time necessary for binding of antibody Y13-259 to the membranes in a ras-dependent manner. The mechanism of **inhibition** appeared to be steric in nature because antibody Y13-259 neutralized ras **p21** bound to a stable GTP analogue. Monoclonal antibodies Y13-4 and Y13-128 also **inhibited** yeast adenylate cyclase activity, and the epitopes for both the these antibodies were localized to ras region 65-75. However, the ras residues essential for binding of antibodies Y13-4 and Y13-128 to ras **p21** (positions 65, 66, 68 and 75) were different from those essential for binding of antibody Y13-259 (positions 63, 65, 66, 67, 70 and 73). These results indicate that residues 63-75 constitute a major neutralizing epitope on ras **p21**.

1988

4/3,AB/57 (Item 44 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

05660456 BIOSIS NO.: 000084008861
CRYSTALLOGRAPHIC STUDY OF ENDOGENOUS ALPHA AMYLASE **INHIBITOR** FROM WHEAT
AUTHOR: MAEDA K; SATO M; KATO Y; TANAKA N; HATA Y; KATSUBE Y; MATSUBARA H
AUTHOR ADDRESS: CENTRAL RES. LAB., NISSHIN FLOUR MILLING CO. LTD., 5-3-1 TSURUGAOKA, OHI-MACHI, IRUMA-GUN, SAITAMA 354, JPN.

JOURNAL: J MOL BIOL 193 (4). 1987. 825-826. **1987**
FULL JOURNAL NAME: Journal of Molecular Biology
CODEN: JMOBA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Endogenous .alpha.-amylase **inhibitor** from wheat has been crystallized by a microdialysis method. There are two forms of monoclinic crystal in a microdialysis cell with a space group of **P21**. The unit cell dimensions are a = 43.5 .ANG., b = 64.8 .ANG., c = 32.2 .ANG., .beta. = 113.degree. for the rod-like crystal, and a = 42.5 .ANG., b = 65.2 .ANG., c = 32.2 .ANG. .beta. = 112.degree. for the plate-like crystal. The former is suitable for structure analysis because it gives the sharp diffraction beyond 2.0 .ANG. resolution, and the latter tends to form a twin crystal. A heavy-atom derivative has been successfully prepared with the heavy-atom reagent K_2PtCl_4 and structure analysis is in progress.

1987

4/3,AB/58 (Item 45 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

04644920 BIOSIS NO.: 000079057957
PYRONES 10. LATEROPYRONE A NEW ANTIBIOTIC FROM THE FUNGUS FUSARIUM-LATERITIUM
AUTHOR: BUSHNELL G W; POULTON G A; LI Y-L
AUTHOR ADDRESS: DEP. CHEMISTRY, UNIV. VICTORIA, VICTORIA, B.C., CANADA V8W 2Y2.
JOURNAL: CAN J CHEM 62 (11). 1984. 2101-2106. **1984**
FULL JOURNAL NAME: Canadian Journal of Chemistry
CODEN: CJCHA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Lateropyrone, 5-hydroxy-9-methoxy-2-methyl-4H,6H-pyrano[3,4-g]-1-benzopyran-4,6-dione-8-carboxylic acid was isolated from cultures of the fungus F. lateritium and has **inhibitory** activity against the growth of a gram-positive bacterium and a yeast. A crystal structure of the dimethyl derivative of lateropyrone was determined. The crystals are monoclinic, space group **P21**/c, with a = 9.663(4), b = 22.317(9), c = 7.747(5) .ANG., .beta. = 113.03(4).degree., Dc = 1.496 g cm-3, V = 1538(1) .ANG.3, T = 25.degree. C, $C_{17}H_{14}O_8$. The structure was refined to R = 0.0543 by least squares using 2100 observed, independent reflections measured on a 4-circle diffractometer, to obtain 241 parameters. The linearly fused tricyclic ring system is only approximately planar. In- and out-of-plane distortions are rationalized in terms of molecular overcrowding.

1984

4/3,AB/59 (Item 46 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

04636551 BIOSIS NO.: 000079049588
A PRODUCT OF YEAST RAS-2 GENE IS A GUANINE NUCLEOTIDE BINDING PROTEIN
AUTHOR: TAMANOI F; WALSH M; KATAOKA T; WIGLER M
AUTHOR ADDRESS: COLD SPRING HARBOR LABORATORY, P.O. BOX 100, COLD SPRING HARBOR, N.Y. 11724.
JOURNAL: PROC NATL ACAD SCI U S A 81 (22). 1984. 6924-6928. **1984**
FULL JOURNAL NAME: Proceedings of the National Academy of Sciences of the

United States of America
CODEN: PNASA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Saccharomyces cerevisiae contains 2 genes, RAS1 and RAS2, which show remarkable homology to mammalian ras genes. To characterize these gene products, the RAS2 gene in yeast was expressed using an inducible GAL10 promoter. After labeling with [35S]methionine and immunoprecipitating with a monoclonal antibody Y13-259, which reacts with **p21** encoded by mammalian ras genes, a major band having an apparent MW of 41,000 was detected. This band was also identified in cell-free translation products of polyadenylylated RNA extracted from yeast cells grown in the presence of galactose. Crude extracts of cells expressing the RAS2 gene exhibited guanine nucleotide binding activity. This was detected by incubation with [3H]GDP followed by immunoprecipitation with the antibody Y13-259. The binding of labeled GDP was **inhibited** by a 20-fold excess of GDP, GTP, and, to a lesser extent, by UTP, a characteristic similar to that possessed by the mammalian ras proteins. The activity of the yeast protein differs from that of the mammalian proteins in its strong dependence on temperature. The guanine nucleotide binding activity provides an assay to purify the yeast protein.

1984

4/3,AB/60 (Item 47 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

02440714 BIOSIS NO.: 000066023258
THE CRYSTAL STRUCTURE OF COLCHICINE A NEW APPLICATION OF MAGIC INTEGERS TO MULTIPLE SOLUTION DIRECT METHODS
AUTHOR: LESSINGER L; MARGULIS T N
AUTHOR ADDRESS: DEP. CHEM., BARNARD COLL., COLUMBIA UNIV., NEW YORK, N.Y. 10027, USA.
JOURNAL: ACTA CRYSTALLOGR SECT B STRUCT CRYSTALLOGR CRYST CHEM 34 (2). 1978 578-584. **1978**
FULL JOURNAL NAME: Acta Crystallographica Section B Structural Crystallography and Crystal Chemistry
CODEN: ACBCA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The mitotic spindle **inhibitor** colchicine, C22H25NO6, crystallizes as a dihydrate in space group **P21**, a = 17.08, b = 10.70, c = 13.88 .ANG., .beta. = 117.9.degree., Z = 4 (C22H25NO6.cntdot.2H2O)/unit cell. The crystal structure was solved by a multiple solution direct method in which unknown starting phases .phi.i are represented using 'magic integers': .phi.i = mix. An appropriate choice of integers mi and sampling of the variable x allows a drastic reduction in computing time and a great increase in structure-solving capability compared to the widely used method in which all unknown phases are permuted among the 4 values 45, 135, 225, 315.degree.. The crystal structure of colchicine dihydrate was refined by least squares to R = 0.052 for 2322 observed X-ray reflections. The 2 independent colchicine molecules have very similar conformations in the crystal. The troponoid rings have alternating bond lengths, and are not precisely planar. These rings make dihedral angles with the planar benzene rings of 53.degree. in one molecule of colchicine, 51.degree. in the other. The 4 independent water molecules are all found in a distinct region in the crystal, which is held together by a complex hydrogen-bond network. Two methoxy-group O atoms of colchicine act as hydrogen-bond acceptors, the one on the troponoid ring participating in a bifurcated H bond.

1978

4/3,AB/61 (Item 48 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

02156272 BIOSIS NO.: 000063071277
A SOYBEAN TRYPSIN **INHIBITOR** CRYSTALLIZATION AND X-RAY CRYSTALLOGRAPHIC STUDY
AUTHOR: HWANG D L; FOARD D E; WEI C H
JOURNAL: J BIOL CHEM 252 (3). 1977 1099-1101. **1977**
FULL JOURNAL NAME: Journal of Biological Chemistry
CODEN: JBCHA
RECORD TYPE: Abstract

ABSTRACT: Five trypsin and .alpha.-chymotrypsin **inhibitors** which have low MW (6800-8600) and are present in soybean seeds of the 'Tracy' cultivar were isolated and purified and single crystals which give X-ray diffraction data beyond 3-.ANG. spacings were obtained from one of them. The trypsin **inhibitor** crystallizes in a monoclinic unit cell of symmetry **P21** and dimensions a = 25.919(7) .ANG., b = 43.23(1).ANG., c = 19.905(5) .ANG., and .beta. = 103.63(2).degree.. The asymmetric unit contains 1 molecule of MW 6800. The crystal, which was found to be unusually stable to X-radiation, has a solvent content of approximately 26% by volume.

1977
? ds

Set	Items	Description
S1	7259	P21 AND (INHIBIT?)
S2	5082	S1 AND PY<2000
S3	65	S2 AND PLANT?
S4	61	RD (unique items)

? s s4 and transgenic?

	61	S4
	73253	TRANSGENIC?
S5	1	S4 AND TRANSGENIC?

? t s5/3,ab/all

5/3,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09928248 98438697 PMID: 9765153
Role of farnesyltransferase in ABA regulation of guard cell anion channels and **plant** water loss.
Pei ZM; Ghassemian M; Kwak CM; McCourt P; Schroeder JI
Department of Biology and Center for Molecular Genetics, University of California, San Diego, La Jolla, CA 92093-0116, USA.
Science (UNITED STATES) Oct 9 **1998**, 282 (5387) p287-90, ISSN 0036-8075 Journal Code: UJ7
Comment in Science. 1998 Oct 9;282(5387) 252-3
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Desiccation of **plants** during drought can be detrimental to agricultural production. The phytohormone abscisic acid (ABA) reduces water loss by triggering stomatal pore closure in leaves, a process requiring ion-channel modulation by cytoplasmic proteins. Deletion of the Arabidopsis farnesyltransferase gene ERA1 or application of farnesyltransferase **inhibitors** resulted in ABA hypersensitivity of guard cell

anion-channel activation and of stomatal closing. ERA1 is expressed in guard cells. Double-mutant analyses of era1 with the ABA-insensitive mutants abi1 and abi2 showed that era1 suppresses the ABA-insensitive phenotypes. Moreover, era1 **plants** exhibited a reduction in transpirational water loss during drought treatment.
? ds

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Set     Items   Description
S1       7259   P21 AND (INHIBIT?)
S2       5082   S1 AND PY<2000
S3         65   S2 AND PLANT?
S4         61   RD (unique items)
S5          1   S4 AND TRANSGENIC?
? s s2 not s3

            5082  S2
              65  S3
      S6    5017  S2 NOT S3
? s s6 and transgenic?

            5017  S6
           73253  TRANSGENIC?
      S7      54  S6 AND TRANSGENIC?
? rd

...examined 50 records  (50)
...completed examining records
      S8      38  RD (unique items)
? t s8/3,ab/all


 8/3,AB/1      (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10442499   20018280   PMID: 10550163
  Ras protein farnesyltransferase: A strategic target for anticancer
therapeutic development.
  Rowinsky EK; Windle JJ; Von Hoff DD
  Institute for Drug Development, Cancer Therapy and Research Center, San
Antonio, TX 78229-3272, USA. erowinski@saci.org
  Journal of clinical oncology (UNITED STATES)  Nov 1999,  17  (11)
 p3631-52,  ISSN 0732-183X  Journal Code: JCO
  Languages: ENGLISH
  Document type: Journal Article; Review; Review, Tutorial
  Record type: Completed
```
  Ras proteins are guanine nucleotide-binding proteins that play pivotal roles in the control of normal and transformed cell growth and are among the most intensively studied proteins of the past decade. After stimulation by various growth factors and cytokines, Ras activates several downstream effectors, including the Raf-1/mitogen-activated protein kinase pathway and the Rac/Rho pathway. In approximately 30% of human cancers, including a substantial proportion of pancreatic and colon adenocarcinomas, mutated ras genes produce mutated proteins that remain locked in an active state, thereby relaying uncontrolled proliferative signals. Ras undergoes several posttranslational modifications that facilitate its attachment to the inner surface of the plasma membrane. The first-and most critical-modification is the addition of a farnesyl isoprenoid moiety in a reaction catalyzed by the enzyme protein farnesyltransferase (FTase). It follows that **inhibiting** FTase would prevent Ras from maturing into its biologically active form, and FTase is of considerable interest as a potential therapeutic target. Different classes of FTase **inhibitors** have been identified that block farnesylation of Ras, reverse Ras-mediated cell transformation in human cell lines, and **inhibit** the growth of human tumor cells in nude mice. In **transgenic** mice with established

tumors, FTase **inhibitors** cause regression in some tumors, which appears to be mediated through both apoptosis and cell cycle regulation. FTase **inhibitors** have been well tolerated in animal studies and do not produce the generalized cytotoxic effects in normal tissues that are a major limitation of most conventional anticancer agents. There are ongoing clinical evaluations of FTase **inhibitors** to determine the feasibility of administering them on dose schedules like those that portend optimal therapeutic indices in preclinical studies. Because of the unique biologic aspects of FTase, designing disease-directed phase II and III evaluations of their effectiveness presents formidable challenges.

8/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10424900 20072247 PMID: 10606231
Combination therapy with the farnesyl protein transferase **inhibitor** SCH66336 and SCH58500 (p53 adenovirus) in preclinical cancer models.
Nielsen LL; Shi B; Hajian G; Yaremko B; Lipari P; Ferrari E; Gurnani M; Malkowski M; Chen J; Bishop WR; Liu M
Tumor Biology, Schering-Plough Research Institute, Kenilworth, New Jersey 07033, USA.
Cancer research (UNITED STATES) Dec 1 **1999**, 59 (23) p5896-901, ISSN 0008-5472 Journal Code: CNF
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
SCH66336 is a p.o.-active, farnesyl protein transferase **inhibitor**. SCH66336 **inhibits** farnesylation of RAS and other proteins in tumor cells and suppresses tumor growth in human xenograft and **transgenic** mouse cancer models in vivo. SCH58500 is a replication-deficient, recombinant adenovirus, which expresses the human p53 tumor suppressor. In preclinical models, SCH58500 has therapeutic efficacy against a wide range of human tumor types containing nonfunctional p53 and enhanced activity in combination with many chemotherapeutic drugs. Here we report that combination therapy with SCH66336 and SCH58500 has synergistic or additive antiproliferative effects on a panel of tumor cells lines in vitro. The efficacy of the three-drug combination of SCH66336, SCH58500, and paclitaxel was also examined in vitro. Each two-drug interaction displayed such marked synergy, the addition of a third drug to the statistical model could only yield additivity. Greater combined efficacy for SCH66336 and SCH58500 was also observed in vivo in the DU-145 human prostate and wap-ras/F **transgenic** mouse cancer models.

8/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10342589 99395218 PMID: 10464022
Design and in vivo analysis of potent non-thiol **inhibitors** of farnesyl protein transferase.
Anthony NJ; Gomez RP; Schaber MD; Mosser SD; Hamilton KA; O'Neil TJ; Koblan KS; Graham SL; Hartman GD; Shah D; Rands E; Kohl NE; Gibbs JB; Oliff AI
Department of Medicinal Chemistry, Merck Research Laboratories, West Point, Pennsylvania 19486, USA.
Journal of medicinal chemistry (UNITED STATES) Aug 26 **1999**, 42 (17) p3356-68, ISSN 0022-2623 Journal Code: J0F
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Inhibitors of farnesyl protein transferase (FPTase) based upon a pseudotripeptide template are described that comprise an imidazole group substituted with a hydrophobic substituent. (1, 5)-Disubstitution of the imidazole group is shown to be the optimal array that leads to potent and

selective **inhibitors** of FPTase. A variety of aryl and isoprenyl substituents are shown to afford effective **inhibitors** and the mechanism by which these compounds **inhibit** FPTase has been investigated. The biochemical behavior of these compounds suggests that they bind to FPTase at the site usually occupied by the protein substrate. In experiments in cell culture, the methyl ester prodrugs of these **inhibitors** are cell permeant and potently **inhibit** the posttranslational modification of H-Ras protein. Additionally, these molecules revert the phenotype of ras transformed cells as evidenced by their ability to slow the growth of ras transformed cell lines in soft agar. One of the **inhibitors**, as its methyl prodrug, was evaluated in two in vivo models of tumor growth. The compound selectively **inhibited** the growth of tumors derived from H-ras transformed cells, in nude mice, and caused the regression of preexisting tumors in an H-ras **transgenic** animal model.

8/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10342054 99380347 PMID: 10449516
Malignant transformation and antineoplastic actions of nonsteroidal antiinflammatory drugs (NSAIDs) on cyclooxygenase-null embryo fibroblasts.
Zhang X; Morham SG; Langenbach R; Young DA
Department of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, New York 14642, USA.
Journal of experimental medicine (UNITED STATES) Aug 16 **1999**, 190 (4) p451-59, ISSN 0022-1007 Journal Code: I2V
Contract/Grant No.: RO1AM-16177, AM, NIADDK
Comment in J Exp Med. 1999 Aug 16;190(4) 445-50
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
In this study, we use primary embryonic fibroblasts derived from cyclooxygenase-deficient **transgenic** embryos to further investigate the role of the two cyclooxygenases, cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2), in the process of neoplastic transformation. Cells with either, neither, or both of the cyclooxygenases were transformed by Ha-ras and/or SV40. Our results show that when a cyclooxygenase enzyme is present, the transformed cells have marked increases in COX-2 and/or COX-1 expression. Nevertheless, each type of cell, deficient in either or both cyclooxygenases, can be readily transformed at almost equal efficiency. Different nonsteroidal antiinflammatory drugs (NSAIDs) were used to examine their possible antineoplastic effects on the transformed cells, which have various levels of expression of COX-1 or COX-2. Our results show that NSAIDs suppress the colony formation in soft agar in a dosage-dependent manner in the absence of the cyclooxygenase(s). Thymidine incorporation and apoptosis analyses further demonstrate that the NSAIDs are effective in the cyclooxygenase-null cells. Our findings with cyclooxygenase knockout cells confirm recent reports that some of the antiproliferative and antineoplastic effects of NSAIDs are independent of the **inhibition** of either COX-1 or COX-2. They also show that transformation is independent of the status of cyclooxygenase expression, suggesting that the involvement of the cyclooxygenases in tumorigenesis may occur at later steps.

8/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10340261 99361946 PMID: 10435593
Role of RhoA activation in the growth and morphology of a murine prostate tumor cell line.
Ghosh PM; Ghosh-Choudhury N; Moyer ML; Mott GE; Thomas CA; Foster BA; Greenberg NM; Kreisberg JI

Department of Pathology, University of Texas Health Science Center, San Antonio 78284, USA.

Oncogene (ENGLAND) Jul 15 **1999**, 18 (28) p4120-30, ISSN 0950-9232 Journal Code: ONC

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Prostate cancer cells derived from **transgenic** mice with adenocarcinoma of the prostate (TRAMP cells) were treated with the HMG-CoA reductase **inhibitor**, lovastatin. This caused inactivation of the small GTPase RhoA, actin stress fiber disassembly, cell rounding, growth arrest in the G1 phase of the cell cycle, cell detachment and apoptosis. Addition of geranylgeraniol (GGOL) in the presence of lovastatin, to stimulate protein geranylgeranylation, prevented lovastatin's effects. That is, RhoA was activated, actin stress fibers were assembled, the cells assumed a flat morphology and cell growth resumed. The following observations support an essential role for RhoA in TRAMP cell growth: (1) TRAMP cells expressing dominant-negative RhoA (T19N) mutant protein displayed few actin stress fibers and grew at a slower rate than controls (35 h doubling time for cells expressing RhoA (T19N) vs 20 h for untransfected cells); (2) TRAMP cells expressing constitutively active RhoA (Q63L) mutant protein displayed a contractile phenotype and grew faster than controls (13 h doubling time). Interestingly, addition of farnesol (FOL) with lovastatin, to stimulate protein farnesylation, prevented lovastatin-induced cell rounding, cell detachment and apoptosis, and stimulated cell spreading to a spindle shaped morphology. However, RhoA remained inactive and growth arrest persisted. The morphological effects of FOL addition were prevented in TRAMP cells expressing dominant-negative H-Ras (T17N) mutant protein. Thus, it appears that H-Ras is capable of inducing cell spreading, but incapable of supporting cell proliferation, in the absence of geranylgeranylated proteins like RhoA.

8/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10307888 98334387 PMID: 9671312

Expression of a p53 mutant in the epidermis of **transgenic** mice accelerates chemical carcinogenesis.

Wang XJ; Greenhalgh DA; Jiang A; He D; Zhong L; Medina D; Brinkley BR; Roop DR

Department of Cell Biology, Baylor College of Medicine, Houston, Texas 77030, USA.

Oncogene (ENGLAND) Jul 9 **1998**, 17 (1) p35-45, ISSN 0950-9232 Journal Code: ONC

Contract/Grant No.: CA41424, CA, NCI; CA52607, CA, NCI

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

To develop an in vivo model for studying the role of the p53 tumor suppressor in skin carcinogenesis, a murine p53(172H) mutant (equivalent to human p53(175H)) was expressed in the epidermis of **transgenic** mice, utilizing a targeting vector based on the human keratin 1 gene (HK1.p53m). HK1.p53m mice developed normally and did not exhibit an obvious epidermal phenotype or develop spontaneous tumors. However, these mice demonstrated an increased susceptibility to a two-stage chemical carcinogenesis protocol, with the rate of formation and number of papillomas being dramatically increased as compared to non-**transgenic** controls. The majority of papillomas in control mice regressed after termination of 12-O-tetradecanoylphorbol-13-acetate (TPA) treatment, whereas p53m papillomas progressed to carcinomas and metastases. In addition, more advanced malignancy, i.e., undifferentiated spindle cell carcinomas, were exclusively observed in p53m mice. Increased bromodeoxyuridine (BrdU) labeling, accompanied by decreased expression of **p21**, was observed in HK1.p53m papillomas. In situ examination of centrosomes in HK1.p53m

papillomas also revealed marked abnormalities, with 75% of the cells containing > or = 3 centrosomes/cell, whereas centrosome numbers in papillomas from control animals remained normal. These data suggest that the accelerated tumorigenesis observed in chemically-treated p53m mice is most likely due to increased genomic instability resulting from an **inhibition** of G1 arrest and abnormal amplification of centrosomes.

8/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10300126 98151505 PMID: 9482878
Human papillomavirus type 16 E6 and E7 oncogenes abrogate radiation-induced DNA damage responses in vivo through p53-dependent and p53-independent pathways.
Song S; Gulliver GA; Lambert PF
McArdle Laboratory for Cancer Research, University of Wisconsin Medical School, 1400 University Avenue, Madison, WI 53706, USA.
Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Mar 3 **1998**, 95 (5) p2290-5, ISSN 0027-8424 Journal Code: PV3
Contract/Grant No.: CA07175, CA, NCI; CA22443, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
E6 and E7 oncoproteins from high risk human papillomaviruses (HPVs) transform cells in tissue culture and induce tumors in vivo. Both E6, which **inhibits** p53 functions, and E7, which **inhibits** pRb, can also abrogate growth arrest induced by DNA-damaging agents in cultured cells. In this study, we have used **transgenic** mice that express HPV-16 E6 or E7 in the epidermis to determine how these two proteins modulate DNA damage responses in vivo. Our results demonstrate that both E6 and E7 abrogate the **inhibition** of DNA synthesis in the epidermis after treatment with ionizing radiation. Increases in the levels of p53 and **p21** proteins after irradiation were suppressed by E6 but not by E7. Through the study of p53-null mice, we found that radiation-induced growth arrest in the epidermis is mediated through both p53-dependent and p53-independent pathways. The abrogation of radiation responses in both E6 and E7 **transgenic** mice was more complete than was seen in the p53-null epidermis. We conclude that E6 and E7 each have the capacity to modulate p53-dependent as well as p53-independent cellular responses to radiation. Additionally, we found that the conserved region (CR) 1 and CR2 domains in E7 protein, which are involved in the inactivation of pRb function and required for E7's transforming function, were also required for E7 to modulate DNA damage responses in vivo. Thus pRb and/or pRb-like proteins likely mediate both p53-dependent and p53-independent responses to radiation.

8/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10299886 98175566 PMID: 9515813
Antitumor effect of a farnesyl protein transferase **inhibitor** in mammary and lymphoid tumors overexpressing N-ras in **transgenic** mice.
Mangues R; Corral T; Kohl NE; Symmans WF; Lu S; Malumbres M; Gibbs JB; Oliff A; Pellicer A
Department of Pathology and Kaplan Cancer Center, New York University Medical Center, New York 10016, USA.
Cancer research (UNITED STATES) Mar 15 **1998**, 58 (6) p1253-9, ISSN 0008-5472 Journal Code: CNF
Contract/Grant No.: 5T32 CA09161, CA, NCI; CA36327, CA, NCI; CA50434, CA, NCI
Languages: ENGLISH
Document type: Journal Article

Record type: Completed

We tested the antineoplastic effect of the farnesyltransferase **inhibitor** L-744,832 in mammary and lymphoid tumors overexpressing the N-ras proto-oncogene in **transgenic** mice. Mice bearing mammary tumors were randomly assigned to receive daily 40 mg/kg s.c. injections of this compound (experimental group, n = 6) or vehicle (control group, n = 6) per day for 5.5 weeks. Treatment with the compound significantly reduced the mammary tumor mean growth rate in the experimental group (-0.7 mm3/day), as compared with the control group (+28.2 mm3/day; P < 0.001). There was a significant difference in lymphoma incidence at the end of the treatment between the experimental (0 of 6) and the control (3 of 6) groups (P < 0.05). Therefore, this compound is effective in treating in vivo mammary carcinomas and lymphomas in which an activated N-Ras pathway drives tumorigenesis. The number of apoptotic figures in mammary tumors was significantly higher (P = 0.04) in the experimental (14.7 +/- 8.1) than it was in the control (5.7 +/- 3.5) group, indicating that apoptotic induction could contribute to the mechanism of antitumor activity of this compound. We analyzed the level of processing of N-Ras and H-Ras after immunoprecipitation and Western blotting of protein extracts obtained from mammary tumors treated with L-744,832 or vehicle, either in vivo or in vitro (after primary culture of the same tumors), and from several in vitro treated control cell lines. In all compound-treated mammary tumors and cell lines, H-Ras was mostly unprocessed (more so after in vitro than after in vivo treatment), whereas N-Ras remained mostly processed. Both H-Ras and N-Ras remained fully processed in all vehicle-treated samples. These findings are consistent with a less intense antineoplastic effect of the treatment with the compound in our N-ras model than the effect previously reported for the same compound in H-ras **transgenics**. In addition, the finding that, in compound-treated mammary tumors, the N-Ras protein remains mainly processed suggests that, in our model, other proteins in addition to Ras may be a target for the compound. Our results and the previous findings of frequent N-ras activation in human hematopoietic malignancies support a role for L-744,832 in the treatment of lymphomas and of mammary carcinomas with an activated N-Ras pathway, as well as the testing of a farnesyl protein transferase **inhibitor** in humans to establish its clinical relevance.

8/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10293730 97454668 PMID: 9309147

Inhibitors of isoprenylation of ras **p21**]

Yoshimatsu K

Tsukuba Research Laboratories, Eisai Co., Ltd.

Gan to kagaku ryoho (JAPAN) Sep **1997**, 24 (11) p1495-502,
ISSN 0385-0684 Journal Code: 6T8

Languages: JAPANESE

Document type: Journal Article; Review; Review, Tutorial

Record type: Completed

Posttranslational modification and membrane localization are critical for the function of products of ras oncogenes which are frequently founded to be mutated in human tumors. Farnesylation by farnesyltransferase (FTase) is the first and obligatory step in the processing of ras **p21**, and FTase has attracted attention as a new target of anticancer agents. Many FTase **inhibitors** have been identified or synthesized in random screening, and studies on FPP analogs, CAAX analogs, and bisubstrate analogs. These **inhibitors** induced flat reversion and **inhibited** the anchorage-independent growth of ras transformant and ras-mutated human tumor cells through the **inhibition** of posttranslational modification of ras **p21**. B1086, L-739,749, L-744,832 and FTI-276, which are CAAX analogs, were reported to show **inhibition** of tumor growth in ras-mutated human tumor xenograft models and to induce regression of mammary and salivary carcinoma in ras **transgenic** mouse model. FTase **inhibitors** have the potential to be developed as therapy for

ras-mutated human tumors. On the other hand, it has been reported that K-ras 4B **p21** could be modified by geranylgeranyltransferase (GGTase). Therefore, GGTase **inhibitors** have also been evaluated in addition to FTase **inhibitors**.

8/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10237375 99310958 PMID: 10381644
Truncated products of the vestigial proliferation gene induce apoptosis.
de Bor VV; Delanoue R; Cossard R; Silber J
Institut Jacques Monod, Tour 43, 2 Place Jussieu, 75251 Paris, France.
Cell death and differentiation (ENGLAND) Jun **1999**, 6 (6) p557-64, ISSN 1350-9047 Journal Code: C7U
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

The vestigial (vg) gene in D. melanogaster, whose mutant phenotype is characterized by wing atrophy, encodes a novel nuclear protein involved in cell proliferation. The original vg mutant (vgBG) displays massive apoptosis in the wing imaginal disc. Here we tested the hypothesis that the vg mutant phenotype could be due: (i) to lack of cell proliferation in null mutants due to the absence of the Vg product and, (ii) to apoptosis in vgBG and other mutants due to the presence of a major Vg truncated product. In agreement with our hypothesis no cell death was observed in null vg mutants, and the anticell death baculovirus P35 product is unable to rescue the mutant phenotype caused by absence of the Vg product. In addition, expression of the antiproliferative gene dacapo, the homolog of **p21**, induces a mutant wing phenotype without inducing cell death. In contrast the wing phenotype of the original vg mutant could be reproduced by the ectopic expression of the reaper cell death gene when expressed by vg regulatory sequences. In agreement with the hypothesis, the classic vg mutant spontaneously displays an increase in reaper expression in the wing disc and its phenotype can be partially rescued by the P35 product. Finally, we showed that ectopic expression of a truncated Vg product is able on its own to induce ectopic cell death and reaper expression. Our results shed new light on the function of the vg gene, in particular, they suggest that the normal and truncated products affect vg target genes in different ways.

8/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10184723 99251709 PMID: 10319991
Heterozygosity of p21WAF1/CIP1 enhances tumor cell proliferation and cyclin D1-associated kinase activity in a murine mammary cancer model.
Jones JM; Cui XS; Medina D; Donehower LA
Division of Molecular Virology, Baylor College of Medicine, Houston, Texas 77030, USA.
Cell growth & differentiation (UNITED STATES) Apr **1999**, 10 (4) p213-22, ISSN 1044-9523 Journal Code: AYH
Contract/Grant No.: CA54897, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

The **p21**(WAF1/cIP1) cyclin-dependent kinase (cdk) **inhibitor** is a regulator of the G(1)-S cell cycle checkpoint. Despite the importance of **p21** in cell cycle **inhibition**, its role as a tumor suppressor is uncertain. **p21** mutations are infrequent in human tumors, and **p21** null mice exhibit no increased tumor incidence. To ascertain whether **p21** could influence tumor formation or progression in the context of other oncogenic stimuli, we crossed **p21**-deficient mice with mammary tumor susceptible Wnt-1 **transgenic** mice. The **p21**

+/+, **p21**+/-, and **p21**-/- Wnt-1 **transgenic** female offspring were monitored for mammary tumor incidence and growth rates. **p21** status had no effect on the age at which mammary tumors formed. However, **p21**+/- mammary tumors grew significantly faster than **p21**+/+ and **p21** -/- mammary tumors. The increased growth rates were confirmed by mitotic index counts and by BrdUrd labelling assays, indicating that a significantly higher percentage of **p21**+/- tumor cells were in S phase and mitosis than their **p21**+/+ and **p21** -/- counterparts. Moreover, cyclin D1-associated phosphorylation of retinoblastoma protein was significantly increased in **p21**+/- tumor lysates compared with **p21**+/+ and **p21** -/- lysates. These results are consistent with data indicating that reduced levels of **p21** can facilitate cyclin/cdk complex formation while enhancing cdk activity. Thus, a reduction of **p21** dosage may promote tumor progression in the presence of other oncogenic initiators. The dependence of **p21** on prior oncogenic stimuli for its tumor-promoting activities suggests that it may behave as a tumor modifier gene rather than as a tumor suppressor gene.

8/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10175658 99308595 PMID: 10380888
Effect of p21waf1/cip1 transgene on radiation induced apoptosis in T cells.
Fotedar R; Brickner H; Saadatmandi N; Rousselle T; Diederich L; Munshi A; Jung B; Reed JC; Fotedar A
Institut de Biologie Structurale JP Ebel, Grenoble, France.
Oncogene (ENGLAND) Jun 17 **1999**, 18 (24) p3652-8, ISSN 0950-9232 Journal Code: ONC
Contract/Grant No.: AI31453, AI, NIAID; CA74435, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The cyclin kinase **inhibitor** p21WAF1/Cip1 is upregulated by the tumor suppressor p53. While **p21** is central for the G-1 arrest mediated by p53, it is still unclear if **p21** also functions as a downstream effector of p53 dependent apoptosis. Apoptosis induced by DNA damage but not dexamethasone is p53 dependent in thymocytes. To investigate the physiological role of **p21** in apoptosis, we have generated **transgenic** mice in which the **p21** transgene is targeted for restricted expression in the T cell lineage. Thymocytes from **p21** **transgenic** mice were hypersensitive to cell death induced by DNA damaging agents such as ionizing radiation and UV, but not be dexamethasone. Irradiated **p21** **transgenic** thymocytes had approximately twofold more apoptotic cells as compared to irradiated age matched littermate control mice. Radiation induced death is comparable in thymocytes from **p21** + Bcl2 + double **transgenic** mice and age matched littermate controls, indicating that the Bcl2 transgene rescues the radiation hypersensitivity imposed by **p21**. However, thymocytes from p53-/- mice even when they expressed the **p21** transgene, were resistant to death induced by radiation. Together these results show that thymocytes from **p21** **transgenic** mice are hypersensitive to radiation induced programmed cell death and suggest that the radiation hypersensitivity of **p21** **transgenic** thymocytes involves p53 dependent pathway and signals in addition to **p21**.

8/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10018913 99124694 PMID: 9925645
p21 (CIP1) and p57(KIP2) control muscle differentiation at the myogenin step.
Zhang P; Wong C; Liu D; Finegold M; Harper JW; Elledge SJ

Howard Hughes Medical Institute, Baylor College of Medicine, Houston, Texas 77030 USA.
Genes & development (UNITED STATES) Jan 15 **1999**, 13 (2) p213-24, ISSN 0890-9369 Journal Code: FN3
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Cell-cycle arrest is thought to be required for differentiation of muscle cells. However, the molecules controlling cell-cycle exit and the differentiation step(s) dependent on cell-cycle arrest are poorly understood. Here we show that two Cdk **inhibitors**, **p21**(CIP1) and p57(KIP2), redundantly control differentiation of skeletal muscle and alveoli in the lungs. Mice lacking both **p21** and p57 fail to form myotubes, display increased proliferation and apoptotic rates of myoblasts, and display endoreplication in residual myotubes. This point of arrest during muscle development is identical to that of mice lacking the myogenic transcription factor myogenin, indicating a role for cell-cycle exit in myogenin function. Expression of myogenin, **p21**, and p57 is parallel but independent, and in response to differentiation signals, these proteins are coordinately regulated to trigger both cell-cycle exit and a dependent muscle-specific program of gene expression to initiate myoblast terminal differentiation and muscle formation.

8/3,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09926066 98445376 PMID: 9770491
Inhibition of myogenesis by transforming growth factor beta is density-dependent and related to the translocation of transcription factor MEF2 to the cytoplasm.
De Angelis L; Borghi S; Melchionna R; Berghella L; Baccarani-Contri M; Parise F; Ferrari S; Cossu G
Istituto Pasteur Fondazione Cenci-Bolognetti, Dipartimento di Istologia ed Embriologia Medica, Universita di Roma La Sapienza, Via A, Scarpa 14, 00161 Rome, Italy.
Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Oct 13 **1998**, 95 (21) p12358-63, ISSN 0027-8424 Journal Code: PV3
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Transforming growth factor beta (TGF-beta) was found to **inhibit** differentiation of myogenic cells only when they were grown to high density. **Inhibition** also occurred when myogenic cells were cocultured with other types of mesenchymal cells but not when they were cocultured with epithelial cells. It is therefore possible that some density-dependent signaling mediates the intracellular response to TGF-beta. Within 30 min of treatment, TGF-beta induced translocation of MEF2, but not MyoD, myogenin, or **p21** , to the cytoplasm of myogenic cells grown to high density. Translocation was reversible on withdrawal of TGF-beta. By using immune electron microscopy and Western blot analysis on subcellular fractions, MEF2 was shown to be tightly associated with cytoskeleton membrane components. To test whether MEF2 export from the nucleus was causally related to the **inhibitory** action of TGF-beta, we transfected C2C12 myoblasts with MEF2C containing the nuclear localization signal of simian virus 40 large T antigen (nlsSV40). Myogenic cells expressing the chimerical MEF2C/nlsSV40, but not wild-type MEF2C, retained this transcription factor in the nucleus and were resistant to the **inhibitory** action of TGF-beta. We propose a mechanism in which the **inhibition** of myogenesis by TGF-beta is mediated through MEF2 localization to the cytoplasm, thus preventing it from participating in an active transcriptional complex.

8/3,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09907903 99025876 PMID: 9810004
Antitumor activity of SCH 66336, an orally bioavailable tricyclic **inhibitor** of farnesyl protein transferase, in human tumor xenograft models and wap-ras **transgenic** mice.
Liu M; Bryant MS; Chen J; Lee S; Yaremko B; Lipari P; Malkowski M; Ferrari E; Nielsen L; Prioli N; Dell J; Sinha D; Syed J; Korfmacher WA; Nomeir AA; Lin CC; Wang L; Taveras AG; Doll RJ; Njoroge FG; Mallams AK; Remiszewski S; Catino JJ; Girijavallabhan VM; Bishop WR; et al
Department of Biological Research-Oncology, Schering-Plough Research Institute, Kenilworth, New Jersey 07033, USA.
Cancer research (UNITED STATES) Nov 1 **1998**, 58 (21) p4947-56, ISSN 0008-5472 Journal Code: CNF
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
We have been developing a series of nonpeptidic, small molecule farnesyl protein transferase **inhibitors** that share a common tricyclic nucleus and compete with peptide/protein substrates for binding to farnesyl protein transferase. Here, we report on pharmacological and in vivo studies with SCH 66336, a lead compound in this structural class. SCH 66336 potently **inhibits** Ha-Ras processing in whole cells and blocks the transformed growth properties of fibroblasts and human tumor cell lines expressing activated Ki-Ras proteins. The anchorage-independent growth of many human tumor lines that lack an activated ras oncogene is also blocked by treatment with SCH 66336. In mouse, rat, and monkey systems, SCH 66336 has excellent oral bioavailability and pharmacokinetic properties. In the nude mouse, SCH 66336 demonstrated potent oral activity in a wide array of human tumor xenograft models including tumors of colon, lung, pancreas, prostate, and urinary bladder origin. Enhanced in vivo efficacy was observed when SCH 66336 was combined with various cytotoxic agents (cyclophosphamide, 5-fluorouracil, and vincristine). In a Ha-Ras **transgenic** mouse model, prophylactic treatment with SCH 66336 delayed tumor onset, reduced the average number of tumors/mouse, and reduced the average tumor weight/animal. In a therapeutic mode in which gavage treatment was initiated after the **transgenic** mice had developed palpable tumors, significant tumor regression was induced by SCH 66336 in a dose-dependent fashion. This was associated with increased apoptosis and decreased DNA synthesis in tumors of animals treated with SCH 66336. Enhanced efficacy was also observed in this model when SCH 66336 was combined with cyclophosphamide. SCH 66336 is presently being evaluated in Phase I clinical trials.

8/3,AB/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09898478 98326598 PMID: 9663465
Butyrate-induced G1 arrest results from **p21**-independent disruption of retinoblastoma protein-mediated signals.
Vaziri C; Stice L; Faller DV
Cancer Research Center, Boston University School of Medicine, Massachusetts 02118, USA.
Cell growth & differentiation (UNITED STATES) Jun **1998**, 9 (6) p465-74, ISSN 1044-9523 Journal Code: AYH
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
When treated with millimolar concentrations of butyrate, many cell types undergo growth arrest in the G1 phase of the cell cycle. However, the molecular basis of butyrate-induced G1 arrest has not been elucidated. We have investigated the molecular mechanisms of butyrate-induced G1 arrest in synchronized cultures of untransformed 3T3 fibroblasts. We tested the

hypothesis that butyrate-induced growth arrest might be mediated by the **p21** cyclin-dependent kinase **inhibitor**. Sodium butyrate-treated 3T3 cells did, indeed, express elevated levels of **p21** mRNA under conditions of G1 arrest. Surprisingly, however, primary cultures of fibroblasts from **transgenic p21** "knockout" (**p21**-/-) mice and fibroblasts from wild-type **p21**-proficient (**p21**+/+) mice underwent butyrate-induced G1 arrest with similar dose dependencies. Therefore, **p21** expression was not necessary for butyrate-induced G1 arrest. To identify other potential mechanisms of butyrate-induced growth arrest, we analyzed the butyrate sensitivity of key mitogenic signaling events during G1. We found that butyrate **inhibited** the mitogen-dependent transcriptional induction of cyclin D1 and phosphorylation of retinoblastoma (Rb), both in **p21**-proficient 3T3 cells and in **p21**+/+ and **p21** -/- mouse embryo fibroblasts. Butyrate treatment also prevented mitogen-dependent transcriptional induction of cyclin E and expression of cyclin A, cell cycle events that are temporally distal to expression of cyclin D and are necessary for entry into S phase. Abrogation of a requirement for cyclin D/cyclin-dependent kinase-dependent phosphorylation of Rb (by ectopic expression of the human papilloma virus E7 oncoprotein in 3T3 cells) resulted in decreased sensitivity to the antiproliferative actions of butyrate. Overall, these data show that butyrate-induced G1 arrest is, in large part, independent of **p21** induction. Instead, butyrate-induced growth arrest appears to result from perturbation of the Rb signaling axis at the level of or at a stage prior to cyclin D1 expression.

8/3,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09876232 98330886 PMID: 9666457
Biochemical and biological analyses of farnesyl-protein transferase **inhibitors**.
Kohl NE; Koblan KS; Omer CA; Oliff A; Gibbs JB
Department of Cancer Research, Merck Research Laboratories, West Point, PA, USA.
Methods in molecular biology (UNITED STATES) **1998**, 84 p283-91, ISSN 1064-3745 Journal Code: BU3
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The methods outlined in Subheading 3. provide a logical sequence of assays with which to evaluate the biochemical and biological properties of potential FPTase **inhibitors** . The clinical predictability of these assays must await the evaluation of one or more of these compounds in humans.

8/3,AB/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09816320 98340882 PMID: 9676193
A constitutive mutation of ALK5 disrupts cardiac looping and morphogenesis in mice.
Charng MJ; Frenkel PA; Lin Q; Yamada M; Schwartz RJ; Olson EN; Overbeek P ; Schneider MD; Yumada M
Department of Medicine, Baylor College of Medicine, Houston, Texas 77030, USA.
Developmental biology (UNITED STATES) Jul 1 **1998**, 199 (1) p72-9, ISSN 0012-1606 Journal Code: E7T
Erratum in Dev Biol 1998 Oct 15;202(2) 315; Erratum in Note Yumada M[corrected to Yamada M]
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

TGF beta family members are implicated in cardiac organogenesis, growth control, and positional information, including the direction of cardiac looping. However, genetic analysis of TGF beta signaling in mice has been confounded, in some cases, by noncardiac and generalized defects. Hence, deciphering TGF beta function in myocardium would benefit from cardiac-restricted mutations. We developed a constitutively activated type I receptor, ALK5L193A,P194A,T204D, and directed it to embryonic myocardium in **transgenic** mice. Expression of the activated ALK5 gene arrests looping morphogenesis and causes a linear, dilated, hypoplastic heart tube, despite normal expression of Nkx2.5 and dHAND, cardiogenic transcription factors whose absence provokes a similar phenotype. Ventricular hypoplasia was associated with precocious induction of the cyclin-dependent kinase **inhibitor**, **p21** . Thus, an ALK5-sensitive pathway mediates looping, perhaps through control of cardiac myocyte proliferation.

8/3,AB/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09811050 98334482 PMID: 9671407
Lack of relationship between CDK activity and G1 cyclin expression in breast cancer cells.
Sweeney KJ; Swarbrick A; Sutherland RL; Musgrove EA
Cancer Research Program, Garvan Institute of Medical Research, St Vincent's Hospital, Sydney, New South Wales, Australia.
Oncogene (ENGLAND) Jun 4 **1998**, 16 (22) p2865-78, ISSN 0950-9232 Journal Code: ONC
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The G1 cyclins, cyclin D1 and E, are rate limiting for progression through G1 phase of the cell cycle in breast epithelial cells and are oncogenic when expressed in the mammary epithelium of **transgenic** mice. These genes are frequently overexpressed in clinical breast cancer where overexpression appears to be associated with specific disease phenotypes, altered responsiveness to therapeutic intervention and patient survival. In order to investigate the functional correlates of cyclin D1 and cyclin E overexpression we employed a panel of normal, immortalized and neoplastic breast epithelial cell lines to examine the relationships between cyclin gene expression, cyclin-CDK complex formation and CDK activity. In agreement with earlier studies cyclin D1 and E expression varied over an approximately tenfold range among the 18 cell lines studied. There was no apparent relationship, however, between cyclin D1 expression and the in vitro activity of its major kinase partner, Cdk4, although MDA-MB-134 cells displayed the highest level of both cyclin D1 expression and Cdk4 activity. Similarly, there was no significant relationship between cyclin E expression and cyclin E-Cdk2 activity. Fractionation of whole cell lysates by gel filtration chromatography revealed that approximately 90% of the cyclin E protein was present in inactive complexes containing the CDK **inhibitors** **p21** and p27. Much of the small fraction of active cyclin E protein was of very high apparent molecular mass, >400 kDa, suggesting that formation of these complexes is a more important determinant of cyclin E-Cdk2 activity than cyclin E abundance. These data suggest that properties of cyclins D1 and E in addition to their ability to activate Cdk4 and Cdk2 may contribute to the effects of overexpression on the breast cancer phenotype.

8/3,AB/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09679985 98129779 PMID: 9461560
An important role for the retinoblastoma protein in staurosporine-induced G1 arrest in murine embryonic fibroblasts.
Orr MS; Reinhold W; Yu L; Schreiber-Agus N; O'Connor PM

Laboratory of Molecular Pharmacology, Division of Basic Sciences, NCI, National Institutes of Health, Bethesda, Maryland 20892, U[redacted]
Journal of biological chemistry (UNITED STATES) Feb 13 **1998**, 273 (7) p3803-7, ISSN 0021-9258 Journal Code: HIV
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

In this study, we investigated the molecular basis of the ability of staurosporine to induce G1 arrest in murine embryonic fibroblasts (MEFs). We used MEFs from **transgenic** mice lacking several negative regulators of the G1/S phase transition including cells from mice lacking p53, **p21** , retinoblastoma (Rb), or p16 genes. We found that p53 function was not essential for staurosporine-induced G1 arrest. In contrast, MEFs from mice lacking Rb genes showed approximately a 70% reduced capacity to arrest in the G1 phase following staurosporine treatment. In support of a role for Rb in staurosporine-induced G1 arrest, rat embryonic fibroblasts stably overexpressing cyclin D1/Cdk4(R24C) exhibited approximately a 50% reduced G1 arrest response to staurosporine. The role of Rb in determining the degree of staurosporine-induced G1 arrest did not depend on the function of the cyclin-dependent kinase **inhibitors** p16 or **p21** because MEFs lacking either of these genes were still capable of undergoing G1 arrest following staurosporine exposure. Our studies provide evidence of an important role for the Rb protein in determining the degree of staurosporine-induced G1 arrest in the first cell cycle.

8/3,AB/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09617232 98090425 PMID: 9430560
Evolution of neovascularization in mice with overexpression of vascular endothelial growth factor in photoreceptors.
Tobe T; Okamoto N; Vinores MA; Derevjanik NL; Vinores SA; Zack DJ; Campochiaro PA
Department of Ophthalmology, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21287-9277, USA.
Investigative ophthalmology & visual science (UNITED STATES) Jan **1998**, 39 (1) p180-8, ISSN 0146-0404 Journal Code: GWI
Contract/Grant No.: EY05951, EY, NEI; EY09769, EY, NEI; EY10017, EY, NEI; +
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

PURPOSE: To determine the earliest changes that occur in the retina after the onset of ectopic expression of vascular endothelial growth factor (VEGF) by photoreceptors in **transgenic** mice, to characterize the development of neovascularization (NV), and to determine the feasibility of using these mice to test the efficacy of antiangiogenic agents. METHODS: The time course of expression of VEGF transgene mRNA was determined by reverse transcription-polymerase chain reaction (RT-PCR). Histopathologic changes in the retina were investigated by light and electron microscopy and immunocytochemistry. Standard and confocal fluorescence microscopy and image analysis were used to evaluate NV in retinal whole mounts. RESULTS: VEGF transgene mRNA was first detected in the retina by RT-PCR on postnatal day 6 (P6) and increased over the next several days to reach a constant steady-state level between P14 and **P21**. Abnormal cells were seen in the outer nuclear layer on P10 and among photoreceptors on P14; by P18 there were cell aggregates in the subretinal space with evidence of lumen formation. The invading cells were demonstrated to be endothelial cells by staining with an endothelial cell-specific lectin. Whole mounts of retinas perfused with fluorescein-labeled dextran showed a similar sequence of events, with sprouts from retinal vessels in the deep capillary bed seen on P14 and vessels reaching the subretinal space by P18. Confocal and standard fluorescence microscopy and changes in the number and area of neovascular lesions in the subretinal space over time measured by image analysis

suggest gradual enlargement and coalescence of vascular complexes. The subretinal NV was progressively engulfed by the retinal pigmented epithelium. Invasion of blood vessels from the choroid was not identified in any specimen. CONCLUSIONS: These data support the feasibility of using rhodopsin-VEGF **transgenic** mice to study tissue-specific aspects of NV in the retina and to test antiangiogenic agents for **inhibition** of intraretinal and subretinal NV.

8/3,AB/22 (Item 22 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09559472 97359076 PMID: 9216067
Inhibition of cell death by lens-specific overexpression of bcl-2 in **transgenic** mice.
Fromm L; Overbeek PA
Department of Cell Biology, Baylor College of Medicine, Houston, Texas 77030, USA.
Developmental genetics (UNITED STATES) **1997**, 20 (3) p276-87, ISSN 0192-253X Journal Code: DEG
Contract/Grant No.: EY10803, EY, NEI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Previous studies on cell cycle regulation in the ocular lens using **transgenic** mice have shown that inactivation of the retinoblastoma tumor suppressor protein (pRb) can cause postmitotic lens fiber cells to enter the cell cycle. However, when the p53 gene and protein are intact, inactivation of pRb in this terminally differentiated cell type results in cell death, rather than continued proliferation. Since bcl-2 has been shown to act as a cell death repressor, the ability of this gene to block p53-dependent apoptosis in lenses was examined. **Transgenic** mice were generated that overexpress bcl-2 in a lens-specific fashion. Surprisingly, overexpression of bcl-2 was sufficient to interfere with normal fiber cell differentiation, inducing cataracts, microphakia, vacuolization, fiber cell disorganization, and **inhibition** of fiber cell denucleation. The bcl-2 mice were mated to mice exhibiting lens-specific expression of the N-terminal region of simian virus 40 large T antigen (termed truncT). The resulting double **transgenic** mice showed a marked reduction in the truncT-induced fiber cell death. Apoptosis in the truncT mice could also be suppressed by crossing these mice into a p53-deficient background. Either overexpression of bcl-2 or loss of p53 in truncT mice resulted in proliferation of fiber cells around the cortex of the lens. These proliferating fiber cells continue to express beta- and gamma-crystallin proteins, which are normally only expressed following withdrawal from the cell cycle. The p53 protein is known to upregulate expression of certain target genes, including **p21** , a protein that can block cell cycle progression by **inhibition** of cyclin-dependent kinases. In order to assess whether bcl-2 interferes with the transcriptional activation activity of p53, **transgenic** lenses were assayed by in situ hybridization for levels of **p21** expression. Lenses that expressed both truncT and bcl-2 showed elevated **p21**, implying that bcl-2 does not **inhibit** apoptosis by directly **inhibiting** p53, but instead may block a later step in the apoptosis pathway. In addition, overexpression of **p21** is not sufficient to cause apoptosis. These experiments show that the lenses of **transgenic** mice represent a valuable in vivo setting for studies of both induction and **inhibition** of programmed cell death.

8/3,AB/23 (Item 23 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09461506 97192192 PMID: 9040011
Targets of p56(lck) activity in immature thymoblasts: stimulation of the

Ras/Raf/MAPK pathway.
Lin K; Abraham KM
Department of Microbiology and Immunology, University of Maryland School of Medicine, Baltimore 21201, USA.
International immunology (ENGLAND) Feb **1997**, 9 (2) p291-306, ISSN 0953-8178 Journal Code: AY5
Contract/Grant No.: GM-48484, GM, NIGMS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Previous studies suggest that p56(lck) activity influences thymocyte development at a stage prior to TCR alphabeta expression. **Transgenic** mice that express high levels of p56(lck) activity during thymopoiesis develop thymic lymphomas consisting of cells with immature surface phenotypes. We have utilized cell lines derived from lck-induced thymic tumors to define biochemical pathways regulated by p56(lck) activity in immature thymocytes. Here we report that components of the Ras/Raf/MAPK pathway are constitutively activated in these lck-transformed immature thymoblasts. p56(lck) utilizes Shc and Grb2 adaptors to mediate activation of **p21** (ras) in the thymoblast lines by promoting tyrosine phosphorylation of the Shc protein and constitutive interaction between Shc and Grb2. The putative guanine nucleotide exchange factor p95(vav) is also maintained in constitutively tyrosine phosphorylated form as a result of elevated Lck activity. One target of activated Ras, the Raf-1 kinase, is hyperphosphorylated and downstream targets of activated Raf-1, Erk1 and Erk2, are hyperphosphorylated and activated in Lck-transformed thymocytes. Forskolin treatment reverses Raf-1 hyperphosphorylation in the cells and **inhibits** proliferation by blocking G1/S transition. In contrast, conventional protein tyrosine kinase **inhibitors** block proliferation by arresting Lck thymoblasts at G2/M. Lck-mediated stimulation of the Ras/Raf/MAPK pathway is also required to maintain cell viability by preventing programmed cell death. In summary, p56(lck) activity stimulates G1/S transition in immature thymoblasts and maintains cell viability via transduction of constitutive activation signals downstream to components of the Ras/Raf/MAPK pathway.

8/3,AB/24 (Item 24 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09292403 97193345 PMID: 9040936
Cyclin-dependent kinase **inhibitor** expression in pulmonary Clara cells transformed with SV40 large T antigen in **transgenic** mice.
Magdaleno SM; Wang G; Mireles VL; Ray MK; Finegold MJ; DeMayo FJ
Department of Cell Biology, Baylor College of Medicine, Houston, Texas 77030, USA.
Cell growth & differentiation (UNITED STATES) Feb **1997**, 8 (2) p145-55, ISSN 1044-9523 Journal Code: AYH
Contract/Grant No.: HL 47620, HL, NHLBI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Expression of cell cycle regulatory genes in mouse lung was investigated in **transgenic** models for Clara cell transformation. Clara cells were transformed by generating **transgenic** mice in which the SV40 large T antigen was expressed under the control of the mouse Clara cell M(r) 10,000 protein promoter. The resulting lung tumors express the large T antigen in normal Clara cells and in tumors, and these tumors express reduced levels of CC10 mRNA. The expression of cell cycle regulatory protein, p53, and the cyclin-dependent kinase **inhibitors** was analyzed by Northern blot analysis and in situ hybridization throughout the progression of Clara cell transformation in the lung. Increases in specific cyclin-dependent kinase **inhibitor** steady-state mRNA levels were detected in p15, p18, p27, and p57 during tumor progression. The expression of p15, p57, and **p21** mRNAs were verified by in situ hybridization. Using this approach,

regulatory genes have been identified that may be involved in the regulation of Clara cell differentiation.

8/3,AB/25 (Item 25 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09244545 97102800 PMID: 8947040
Loss of Rb activates both p53-dependent and independent cell death pathways in the developing mouse nervous system.
Macleod KF; Hu Y; Jacks T
Center for Cancer Research, Department of Biology, Massachusetts Institute of Technology, Cambridge 02139, USA.
EMBO journal (ENGLAND) Nov 15 **1996**, 15 (22) p6178-88, ISSN 0261-4189 Journal Code: EMB
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Extensive apoptosis occurs in the nervous system of mouse embryos homozygous mutant for a targeted disruption of the retinoblastoma (Rb) gene. This cell death is present in both the central (CNS) and peripheral nervous systems (PNS) and is associated with abnormal S phase entry of normally post-mitotic neurons. Aberrant proliferation in the CNS correlates with increased free E2F DNA binding activity and increased expression of cyclin E, an E2F target gene and critical cell cycle regulator. Cell death in the CNS is accompanied by increased levels of the p53 tumor suppressor gene product and increased expression of the p53 target gene, p21Waf-1/Cip-1. However, induction of p53 is not observed in the PNS of Rb-mutant embryos, nor does loss of p53 function **inhibit** cell death in the PNS. Surprisingly, p21Waf-1/Cip-1 is induced in the sensory ganglia of Rb-mutant embryos in a p53-independent manner. Although loss of p53 gene function prevents cell death in the CNS of Rb-mutant embryos, it does not restore normal proliferative control.

8/3,AB/26 (Item 26 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09221541 96408090 PMID: 8813135
Paradoxical tumor **inhibitory** effect of p53 loss in **transgenic** mice expressing epidermal-targeted v-rasHa, v-fos, or human transforming growth factor alpha.
Greenhalgh DA; Wang XJ; Donehower LA; Roop DR
Department of Cell Biology, Baylor College of Medicine, Houston, Texas 77030, USA.
Cancer research (UNITED STATES) Oct 1 **1996**, 56 (19) p4413-23, ISSN 0008-5472 Journal Code: CNF
Contract/Grant No.: CA52067, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
To investigate the effect of p53 tumor suppressor gene loss in the mouse skin model of multistage carcinogenesis, p53 knockout mice, generated by gene targeting (p53 -/-), were mated to **transgenic** mice expressing v-rasHa (HK1.ras), v-fos (HK1.fos), or human transforming growth factor alpha+HK1.TGFalpha) exclusively in the epidermis, by means of a keratin K1-based targeting vector (HK1). HK1-p53 **transgenic** progeny expressing wild-type p53 alleles (p53 +/+) or hemizygous for the p53 knockout allele (p53+/-) were identical to parental HK1 lines and exhibited neonatal epidermal hyperplasia or wound-associated hyperplasia in adults, together with spontaneous or 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced benign papillomas. Mating to p53-/- did not lead to the expected tumorigenesis in adults. Instead, whereas HK1.ras or HK1.TGFalpha **transgenic** mice null for p53 (HK1.ras-p53-/- and HK1.TGFalpha-p53-/-, respectively) retained the neonatal epidermal hyperplasia phenotype, in

adults, spontaneous and TPA-promoted papilloma formation was blocked. Similarly, wound-associated epidermal hyperplasia/hyperkeratosis, a hallmark of adult HK1.fos phenotypes, was completely absent in HK1.fos-p53 -/- mice. Histological, immunofluorescence, and bromodeoxyuridine labeling analysis of neonatal or adult epidermis in HK1-p53 **transgenic** genotypes +/+, +/-, and -/- for p53 revealed no obvious differences in morphology, expression of keratinocyte differentiation markers, or mitotic index attributed to p53 loss. To determine whether the paradoxical absence of papillomas centered on up-regulation of p53 target genes, WAF1/CIP1/**p21** RNA expression levels were examined in TPA promotion experiments. WAF1/CIP1/**p21** expression increased in response to TPA promotion in all HK1-p53 **transgenic** genotypes regardless of p53 status. However, in HK1-p53 null genotypes, although TPA-induced, p53-independent WAF1/CIP1/**p21** expression was observed, no large increase in expression was associated with the observed paradoxical tumorigenesis block. These data suggest that epidermis is somewhat resistant to the neoplastic effects of p53 loss, possibly possessing several compensatory systems. Alternatively, there may be a requirement forp53 expression in response to TPA or a wound-promotion stimulus in mouse epidermis.

8/3,AB/27 (Item 27 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08902244 96032759 PMID: 7559464
Ventricular expression of a MLC-2v-ras fusion gene induces cardiac hypertrophy and selective diastolic dysfunction in **transgenic** mice.
Hunter JJ; Tanaka N; Rockman HA; Ross J; Chien KR
Department of Medicine, University of California-San Diego, School of Medicine, La Jolla, California 92093, USA.
Journal of biological chemistry (UNITED STATES) Sep 29 **1995**, 270 (39) p23173-8, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: HL36139, HL, NHLBI; HL40569, HL, NHLBI; HL46345, HL, NHLBI; +
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
p21ras has been implicated in the hypertrophic response of cultured cardiac myocytes to defined growth stimuli. To determine if activation of ras-dependent intracellular signaling pathways is sufficient to induce in vivo hypertrophy, **transgenic** mice were created that express oncogenic ras in the cardiac ventricular chamber. Mice homozygous for the transgene displayed morphological, physiological, and genetic markers of marked cardiac muscle hypertrophy. Miniaturized catheterization technology documented a selective prolongation of cardiac relaxation, similar to that seen in early human hypertrophic heart disease. An increase in left atrial mass, in the absence of transgene expression in that chamber, further supported physiologically abnormal left ventricular diastolic function. Histological analysis revealed myofibrillar disarray, indistinguishable from that in hypertrophic cardiomyopathy in man. These studies establish a ras-dependent pathway for hypertrophic heart disease and document the feasibility of mapping in vivo signaling pathways for cardiac hypertrophy and dysfunction by applying in vivo microphysiological assays to genetically manipulated mice. ras-dependent pathways may also be a rational target for developing new approaches to **inhibit** the genesis of hypertrophy in certain pathological settings.

8/3,AB/28 (Item 28 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08898931 95349955 PMID: 7624147
Schwann cells from neurofibromin deficient mice exhibit activation of p21ras, **inhibition** of cell proliferation and morphological changes.
Kim HA; Rosenbaum T; Marchionni MA; Ratner N; DeClue JE

Department of Cell Biology, Neurobiology and Anatomy, University of Cincinnati College of Medicine, Ohio 45267-0521, USA.
Oncogene (ENGLAND) Jul 20 **1995**, 11 (2) p325-35, ISSN 0950-9232 Journal Code: ONC
Contract/Grant No.: CA59268, CA, NCI; NS 28840, NS, NINDS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Schwann cells are thought to be abnormal in type 1 neurofibromatosis (NF1) and to contribute to the formation of benign and malignant tumors in this disease. To test the role of the NF1 gene product neurofibromin as a Ras-GTPase activating protein in Schwann cells, and to study the effect of the loss of neurofibromin on Schwann cell proliferation, we isolated Schwann cells from mice with targeted disruption of NF1. The properties of these neurofibromin deficient cells were strikingly similar to those of v-ras expressing rat Schwann cells with normal levels of neurofibromin. The similarities included: growth **inhibition**, noted as a decrease in cell division in response to glial growth factor 2 (GGF2) and of neuronal contact; morphological changes such as the appearance of elaborated processes; and elevated levels of Ras-GTP. Furthermore, Ras-GTP levels in the neurofibromin deficient Schwann cells were consistently elevated in response to GGF2 treatment. In contrast to these results, introduction of v-ras into a Schwannoma cell line (RN22) led to cell transformation. We conclude that neurofibromin functions as a major regulator of Ras-GTP in Schwann cells; however, mutation in NF1 by itself is unlikely to explain the hyperplasia observed in Schwann cell tumors in NF1 disease.

8/3,AB/29 (Item 29 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08897960 95327673 PMID: 7604020
Dietary lipids and calorie restriction affect mammary tumor incidence and gene expression in mouse mammary tumor virus/v-Ha-ras **transgenic** mice.

Fernandes G; Chandrasekar B; Troyer DA; Venkatraman JT; Good RA
Departments of Medicine, University of Texas Health Science Center, San Antonio 78284-7874, USA.
Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Jul 3 **1995**, 92 (14) p6494-8, ISSN 0027-8424 Journal Code: PV3
Contract/Grant No.: AG-05633-10, AG, NIA; AG-10531-2, AG, NIA; RO1 AG-03417-14, AG, NIA
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
We have studied the effects of food restriction (FR) and substitution of fish oil (FO; omega 3) for corn oil (CO; omega 6) on breast tumor incidence and survival in mouse mammary tumor virus/v-Ha-ras **transgenic** (Onco) mice. The diets were as follows: group 1, 5% (wt/wt) CO fed ad libitum (AL); group 2, 5% CO, restricted calories (40% fewer calories than AL; FR); group 3, 20% CO fed AL; and group 4, 20% FO fed AL. After 3 years, 40% of FR Onco (group 2) mice were alive, whereas there were no survivors in the other three groups. Similarly, tumor incidence was reduced to 27% (5 out of 18) in FR animals (group 2), whereas it was 83% (11 out of 13) in group 1 mice, 89% (16 out of 18) in group 3 mice, and 71% (10 out of 14) in group 4 mice. These protective effects of FR on survival and tumor incidence were paralleled by higher expression of the tumor suppressor gene p53 (wild type) and free-radical scavenging enzymes (catalase and superoxide dismutase) in breast tumors. Immunoblotting showed less ras gene product, **p21** , and increased p53 levels in the tumors of FR mice. In addition, FR decreased RNA levels of c-erbB-2, interleukin 6, and the transgene v-Ha-ras in tumors. In contrast, analysis of hepatic mRNA from tumor-bearing FR mice revealed higher expression of catalase, glutathione peroxidase, and superoxide dismutase. Survival and tumor incidence were not

influenced significantly by dietary supplementation with FO in place of CO. Taken together, our studies suggest that moderate restriction of energy intake significantly **inhibited** the development of mammary tumors and altered expression of cytokines, oncogenes, and free-radical scavenging enzymes.

8/3,AB/30 (Item 30 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08866109 96176221 PMID: 8595876
Targeted in vivo expression of the cyclin-dependent kinase **inhibitor p21** halts hepatocyte cell-cycle progression, postnatal liver development and regeneration.
Wu H; Wade M; Krall L; Grisham J; Xiong Y; Van Dyke T
Department of Biochemistry and Biophysics, University of North Carolina at Chapel Hill, 27599 USA.
Genes & development (UNITED STATES) Feb 1 **1996**, 10 (3) p245-60, ISSN 0890-9369 Journal Code: FN3
Contract/Grant No.: CA46283, CA, NCI; CA65572, CA, NCI; DK42910, DK, NIDDK
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The CDK **inhibitor p21** (WAF-1/CIP-1/SDI-1) has been implicated in DNA damage-induced p53-mediated G1 arrest, as well as in physiological processes, such as cell differentiation and senescence, that do not involve p53 function. To determine the impact of **p21** on normal development and cell-cycle regulation in vivo, we have generated **transgenic** mice that abundantly express **p21** specifically in hepatocytes. During postnatal liver development, when **transgenic** p-21 protein becomes detectable, hepatocyte proliferation is **inhibited** dramatically. This disturbance causes a reduction in the overall number of adult hepatocytes, resulting in aberrant tissue organization, runted liver and body growth, and increased mortality. The **transgenic p21** protein is associated with most, if not all, of the cyclin D1-CDK4 in liver but not significantly with other cyclin/CDK proteins, indicating the importance of cyclin D1-CDK4 function in normal liver development. The appearance of large polyploid nuclei in some hepatocytes indicates that **p21** may also cause arrest during the G2 phase of the cell cycle. Significantly, partial hepatectomy failed to stimulate hepatocytes to proliferate in **p21 transgenic** animals. These results provide the first in vivo evidence that appropriate **p21** levels are critical in normal development and further implicate **p21** in the control of multiple cell-cycle phases.

8/3,AB/31 (Item 31 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08763388 96069817 PMID: 7481802
Uncoupling cell fate determination from patterned cell division in the Drosophila eye.
de Nooij JC; Hariharan IK
Massachusetts General Hospital Cancer Center, Charlestown 02129, USA.
Science (UNITED STATES) Nov 10 **1995**, 270 (5238) p983-5, ISSN 0036-8075 Journal Code: UJ7
Comment in Science. 1995 Nov 10;270(5238) 916-7
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Cell proliferation and cell fate specification are under strict spatiotemporal control in the developing Drosophila eye. Cells excluded from five-cell preclusters synchronously enter a single additional cell cycle, the second mitotic wave, after which the remaining cells are

sequentially recruited. When the second mitotic wave was blocked with the human cyclin-dependent kinase **inhibitor** p21CIP1/WAF1, each cell type was still specified. Hence, cell fate determination is regulated independently of the division pattern of precursor cells. However, the second mitotic wave is needed to generate appropriate numbers of each cell type. Moreover, **p21** can arrest precursor cell proliferation and allow appropriate fate choice in vivo.

8/3,AB/32 (Item 32 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08642530 96071562 PMID: 7585182
Inhibition of farnesyltransferase induces regression of mammary and salivary carcinomas in ras **transgenic** mice.
Kohl NE; Omer CA; Conner MW; Anthony NJ; Davide JP; deSolms SJ; Giuliani EA; Gomez RP; Graham SL; Hamilton K; et al
Department of Cancer Research, Merck Research Laboratories, West Point, Pennsylvania 19486, USA.
Nature medicine (UNITED STATES) Aug **1995**, 1 (8) p792-7, ISSN 1078-8956 Journal Code: CG5
Comment in Nat Med. 1995 Aug;1(8) 747-8
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
For Ras oncoproteins to transform mammalian cells, they must be post-translationally modified with a farnesyl group in a reaction catalysed by the enzyme farnesyl-protein transferase (FPTase). **Inhibitors** of FPTase have therefore been proposed as anti-cancer agents. We show that L-744,832, which mimics the CaaX motif to which the farnesyl group is added, is a potent and selective **inhibitor** of FPTase. In MMTV-v-Ha-ras mice bearing palpable tumours, daily administration of L-744,832 caused tumour regression. Following cessation of treatment, tumours reappeared, the majority of which regressed upon retreatment. No systemic toxicity was found upon necropsy of L-744,832-treated mice. This first demonstration of anti-FPTase-mediated tumour regression suggests that FPTase **inhibitors** may be safe and effective anti-tumour agents in some cancers.

8/3,AB/33 (Item 33 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08642525 96071553 PMID: 7585173
Rational cancer therapy.
Lowy DR; Willumsen BM
Laboratory of Cellular Oncology, National Cancer Institute Bethesda, Mayrland, 20892, USA.
Nature medicine (UNITED STATES) Aug **1995**, 1 (8) p747-8, ISSN 1078-8956 Journal Code: CG5
Comment on Nat Med. 1995 Aug;1(8) 792-7
Languages: ENGLISH
Document type: Comment; Journal Article
Record type: Completed

8/3,AB/34 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12301894 BIOSIS NO.: 200000059761
Effect of elevated levels of ornithine decarboxylase on cell cycle progression in skin.
AUTHOR: Gilmour Susan K(a); Birchler Mary; Smith Mary K; Rayca Kathryn; Mostochuk Judith

AUTHOR ADDRESS: (a)Lankenau Medical Research Center, 100 Lancaster Avenue, Wynnewood, PA**USA
JOURNAL: Cell Growth & Differentiation 10 (11):p739-748 Nov., **1999**
ISSN: 1044-9523
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: By crossing TG.AC v-Ha-ras and K6/ODC **transgenic** mice, we found previously that an activated ras and follicular ornithine decarboxylase (ODC) overexpression cooperate to generate spontaneous tumors in the skin. Cellular proliferation was dramatically increased in the K6/ODC **transgenic** skin, as evidenced by elevated proliferating cell nuclear antigen and Ki67 expression compared with nontransgenic littermates. Keratinocytes isolated from **transgenic** skin also displayed increased clonal growth. Paradoxically, expression of the growth **inhibition**-associated proteins p53, p21Waf1, p27Kip1, and Bax was increased with ODC overexpression in the skin. ODC overexpression did not affect cyclin D/cyclin-dependent kinase 4 (Cdk4)-dependent phosphorylation of retinoblastoma protein but stimulated cyclin E/Cdk2 and cyclin A/Cdk2-associated kinase activity, with minimal effect on the levels of these proteins. Thus, ODC/polyamine-induced activation of cyclin E/Cdk2 and cyclin A/Cdk2-associated kinase activity may cooperate with the ras induction of cyclin D/Cdk4/6-associated retinoblastoma protein phosphorylation to not only stimulate proliferation but ultimately contribute to tumor development.

1999

8/3,AB/35 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12146393 BIOSIS NO.: 199900441242
E1A can provoke G1 Exit that is refractory to **p21** and independent of activating Cdk2.
AUTHOR: Akli Said; Zhan Song; Abdellatif Maha; Schneider Michael D(a)
AUTHOR ADDRESS: (a)Molecular Cardiology Unit, Baylor College of Medicine, One Baylor Plaza, Room 506C, Houston, TX, 77030**USA
JOURNAL: Circulation Research 85 (4):p319-328 Aug. 20, **1999**
ISSN: 0009-7330
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: E1A can evoke G1 exit in cardiac myocytes and other cell types by displacing E2F transcription factors from tumor suppressor "pocket" proteins and by a less well-characterized p300-dependent pathway. Bypassing pocket proteins (through overexpression of E2F-1) reproduces the effect of inactivating pocket proteins (through E1A binding); however, pocket proteins associate with a number of molecular targets apart from E2F. Hence, pocket protein binding by E1A might engage mechanisms for cell cycle reentry beyond those induced by E2F-1. To test this hypothesis, we used adenoviral gene transfer to express various E2F-1 and E1A proteins in neonatal rat cardiac myocytes that are already refractory to mitogenic serum, in the absence or presence of several complementary cell cycle **inhibitors**-p16, **p21**, or dominant-negative cyclin-dependent kinase-2 (Cdk2). Rb binding by E2F-1 was neither necessary nor sufficient for G1 exit, whereas DNA binding was required; thus, exogenous E2F-1 did not merelyfunction by competing for the Rb "pocket." E2F-1-induced G1 exit was blocked by the "universal" Cdk **inhibitor p21** but not by p16, a specific **inhibitor** of

Cdk4/6; **p21** was permissive for E2F-1 induction of cyclins E and A, but prevented their stimulation of Cdk2 kinase activity. In addition, E2F-1-induced G1 exit was blocked by dominant-negative Cdk2. Forced expression of cyclin E induced endogenous Cdk2 activity but not G1 exit. Thus, E2F-1-induced Cdk2 function was necessary, although not sufficient, to trigger DNA synthesis in cardiac muscle cells. In contrast, pocket protein-binding forms of E1A induced G1 exit that was resistant to **inhibition** by **p21**, whereas G1 exit via the E1A p300 pathway was sensitive to **inhibition** by **p21**. Both E1A pathways-via pocket proteins and via p300-upregulated cyclins E and A and Cdk2 activity, consistent with a role for Cdk2 in G1 exit induced by E1A. However, **p21** blocked Cdk2 kinase activity induced by both E1A pathways equally. Thus, E1A can cause G1exit without an increase in Cdk2 activity, if the pocket protein-binding domain is intact. E1A also overrides **p21** in U2OS cells, provided the pocket protein-binding domain is intact; thus, this novel function of E1A is not exclusive to cardiac muscle cells. In summary, E1A binding to pocket proteins has effects beyond those produced by E2F-1 alone and can drive S-phase entry that is resistant to **p21** and independent of an increase in Cdk2 function. This suggests the potential involvement of other endogenous Rb-binding proteins or of alternative E1A targets.

1999

8/3,AB/36 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11466039 BIOSIS NO.: 199800247371
NF-kappaB triggers cell cycle arrest in epidermis via specific induction of the cyclin-dependent kinase **inhibitor** p21Cip1.
AUTHOR: Seitz C S; Deng H; Khavari P A
AUTHOR ADDRESS: Stanford Univ., Stanford, CA**USA
JOURNAL: Journal of Investigative Dermatology 110 (4):p475 April, **1998**
CONFERENCE/MEETING: Annual Meeting of the International Investigative Dermatology Cologne, Germany May 7-10, 1998
SPONSOR: The Society for Investigative Dermatology, Inc.
ISSN: 0022-202X
RECORD TYPE: Citation
LANGUAGE: English
1998

8/3,AB/37 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10668001 BIOSIS NO.: 199799289146
Tissue kallikrein-binding protein reduces blood pressure in **transgenic** mice.
AUTHOR: Chen Li-Mei; Ma Jian-Xing; Liang Yu-Mei; Chao Lee; Chao Julie(a)
AUTHOR ADDRESS: (a)Dep. Biochemistry, Med. Univ. South Carolina, 171 Ashley Ave., Charleston, SC 29425**USA
JOURNAL: Journal of Biological Chemistry 271 (44):p27590-27594 **1996**
ISSN: 0021-9258
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The kallikrein-kinin system participates in blood pressure regulation. One of the kallikrein-kinin system components, kallikrein-binding protein, binds to tissue kallikrein and **inhibits** its activity in vitro. To investigate potential roles of rat kallikrein-binding protein (RKBP) in vivo, we have developed

transgenic mice that express an RKBP gene under the control of the mouse metallothionein metal-responsive promoter. Expression of the transgene, RKBP, was detected in the liver, kidney, lung, heart, pancreas, salivary glands, spleen, brain, testis, and adrenal gland at the mRNA and protein levels. Systolic blood pressures of homozygous **transgenic** mice were 88.5 +- 0.8 mm Hg (mean +- S.E., n = 19, P lt 0.001) for one line and 88.8 +- 1.6 mm Hg (mean +- S.E., n = 19, P lt 0.001) for another, as compared with 100.5 +- 0.8 mm Hg (mean +- S.E., n = 18) for control mice. Direct blood pressure measurements of these **transgenic** mice through an arterial cannula showed similar reductions of blood pressure. Intravenous injection of purified RKBP into mice via a catheter produced a dose-dependent reduction of the mean arterial blood pressure. Our findings suggest that RKBP may function as a vasodilator in vivo, independent of regulating the activity of tissue kallikrein.

1996

8/3,AB/38 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10436260 BIOSIS NO.: 199699057405
P53-Independent apoptosis during mammary tumor progression in C3(1)/SV40 large T antigen **transgenic** mice: Suppression of apoptosis during the transition from preneoplasia to carcinoma.
AUTHOR: Shibata Masa-Aki; Maroulakou Ioanna G; Jorcyk Cheryl L; Gold Lyn G; Ward Jerrold M; Green Jeffrey E(a)
AUTHOR ADDRESS: (a)Lab. Molecular Oncol., National Cancer Inst., NIH, Frederick Cancer Research Development Center,**USA
JOURNAL: Cancer Research 56 (13):p2998-3003 **1996**
ISSN: 0008-5472
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Alterations in apoptosis and associated mechanisms during mammary tumor progression were investigated in **transgenic** mice expressing the SV40 large T antigen (TAG) driven by the rat prostatic steroid-binding protein C3(1) 5'-flanking region. Apoptosis levels, assessed by in situ end labeling, were low in normal mammary epithelial cells, highest in atypical hyperplasias (preneoplastic lesions), and less pronounced in adenocarcinomas. Preneoplastic cells maintain the ability to undergo apoptosis as a mechanism of tumor growth suppression, but this critical control of apoptosis is lost as these lesions progress to carcinomas. These alterations in apoptosis occur during mammary tumor progression in mice containing wild-type p53+/+ genotype as well as in mice with the p53-/- genotype. Thus, apoptosis in this tumor model occurs through a p53-independent mechanism. Because other studies have demonstrated p53-dependent apoptosis in T-AG-induced choroid plexus tumors of **transgenic** mice, we propose that the role of p53 in apoptosis may be tissue-specific. In addition, bcl-2 protein was not expressed in any mammary lesions. SV40 T-AG expression, which correlated with the nuclear p53 protein at all stages of tumor progression, was low in normal mammary epithelial cells, moderately high in atypical hyperplasias, and strongly expressed in adenocarcinomas. Nop53 mutations were found at any stage of mammary adenocarcinoma development, suggesting that tumor progression does not require a dominantly acting p53 mutation in this **transgenic** model. **p21**-Waf1/Cip1, a cyclin-dependent kinase **inhibitor**, was expressed in normal mammary tissue but was not detected in the mammary carcinomas, despite high nuclear accumulation of wild-type p53 protein, suggesting functional loss of p53 due to binding of SV40 T-AG to p53. These findings suggest that suppression of apoptosis during the transition from atypical hyperplasia to

adenocarcinoma appears to be a critical event for mammary cancer development in C3(1)/T-A **transgenic** mice and occurs by p and bcl-2-independent pathways.

1996

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? ds

Set     Items   Description
S1       7259   P21 AND (INHIBIT?)
S2       5082   S1 AND PY<2000
S3         65   S2 AND PLANT?
S4         61   RD (unique items)
S5          1   S4 AND TRANSGENIC?
S6       5017   S2 NOT S3
S7         54   S6 AND TRANSGENIC?
S8         38   RD (unique items)
? s s6 not s7

          5017  S6
            54  S7
     S9   4963  S6 NOT S7
? s s9 and stem?

          4963  S9
        224618  STEM?
    S10     73  S9 AND STEM?
? s s9 and blood?

          4963  S9
       2980921  BLOOD?
    S11    351  S9 AND BLOOD?
? s s10 or s11

            73  S10
           351  S11
    S12    410  S10 OR S11
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...examined 50 records  (50)
...examined 50 records  (100)
...examined 50 records  (150)
...examined 50 records  (200)
...examined 50 records  (250)
...examined 50 records  (300)
...examined 50 records  (350)
...examined 50 records  (400)
...completed examining records
    S13    371  RD (unique items)
? ds

Set     Items   Description
S1       7259   P21 AND (INHIBIT?)
S2       5082   S1 AND PY<2000
S3         65   S2 AND PLANT?
S4         61   RD (unique items)
S5          1   S4 AND TRANSGENIC?
S6       5017   S2 NOT S3
S7         54   S6 AND TRANSGENIC?
S8         38   RD (unique items)
S9       4963   S6 NOT S7
S10        73   S9 AND STEM?
S11       351   S9 AND BLOOD?
S12       410   S10 OR S11
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S13 371 RD (unique items)
? s s13 and gene?

371 S13
3865333 GENE?
S14 221 S13 AND GENE?
? s s14 and expand?

221 S14
83269 EXPAND?
S15 2 S14 AND EXPAND?
? t s15/3,ab/all

15/3,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10405130 20040866 PMID: 10571777
The cyclin kinase **inhibitor** p21WAF1/CIP1 is required for glomerular hypertrophy in experimental diabetic nephropathy.
Al-Douahji M; Brugarolas J; Brown PA; Stehman-Breen CO; Alpers CE; Shankland SJ
Department of Medicine, University of Washington, School of Medicine, Seattle, Washington, USA.
Kidney international (UNITED STATES) Nov **1999**, 56 (5) p1691-9, ISSN 0085-2538 Journal Code: KVB
Contract/Grant No.: DK47659, DK, NIDDK; DK51096, DK, NIDDK; DK52121, DK, NIDDK
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
BACKGROUND: Diabetic nephropathy is characterized by glomerular hypertrophy. We have recently shown that experimental diabetes mellitus is associated with an increase in glomerular expression of the cyclin kinase **inhibitor** p21WAF1/CIP1 (**p21**). Furthermore, in vitro glucose-induced mesangial cell hypertrophy is also associated with an up-regulated expression of **p21** . In this study, we tested the hypothesis that **p21** mediates diabetic glomerular hypertrophy in vivo. METHODS: Experimental diabetes mellitus was induced by streptozotocin in mice in which **p21** was **genetically** deleted (**p21** -/-) and in wild-type mice (**p21** +/+). Kidney biopsies were obtained from diabetic and control (citrate injected) **p21** +/+ and **p21** -/- mice at day 60. The tissue was used for morphologic studies of glomerular size (measured by computer image-analysis system), glomerular cellularity (cell count), glomerular matrix expansion (silver stain), apoptosis (TUNEL), and expression of transforming growth factor-beta1 (TGF-beta1) by in situ hybridization. RESULTS: The glomerular tuft area increased 11.21% in diabetic **p21** +/+ mice at day 60 compared with control (3329.98 +/- 244.05 micrometer(2) vs. 2994. 39 +/- 176.22 micrometer(2), P = 0.03), and the glomerular cell count did not change in diabetic **p21** +/+ mice at day 60 compared with the control. These findings are consistent with glomerular hypertrophy. In contrast, the glomerular tuft area did not increase in diabetic **p21** -/- mice at day 60 compared with the control (3544.15 +/- 826.49 vs. 3449.15 +/- 109.65, P = 0.82), nor was there an increase in glomerular cell count (41.41 +/- 13.18 vs. 46.95 +/- 3.00, P = 0.43). Diabetic **p21** +/+ mice, but not **p21** -/- mice, developed an increase in proteinuria at day 60 compared with the control. Tubular cell proliferation, measured by proliferating cell nuclear antigen immunostaining, was increased in both diabetic **p21** +/+ (2.1-fold) and **p21** -/- (7.61-fold) mice compared with controls. Glomerular cell apoptosis did not increase in diabetic mice. Although glomerular TGF-beta1 mRNA levels increased in both strains of diabetic mice at day 60, the glomerular matrix did not **expand** . CONCLUSIONS: Hyperglycemia was associated with glomerular hypertrophy in **p21** +/+ mice. Despite the increase in TGF-beta1 mRNA, diabetic **p21** -/- mice did not develop

glomerular hypertrophy, providing evidence that the cyclin kinase **inhibitor p21** may be required for diabetic glomerular hypertrophy induced by TGF-betal. The loss of **p21** increases tubular but not glomerular cell proliferation in diabetic nephropathy. The absence of glomerular hypertrophy appears protective of renal function in diabetic mice.

15/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10168555 99248638 PMID: 10231856
p57Kip2 expression is enhanced during mid-cardiac murine development and is restricted to trabecular myocardium.
Kochilas LK; Li J; Jin F; Buck CA; Epstein JA
Division of Pediatric Cardiology, Children's Hospital of Philadelphia, Pennsylvania, USA.
Pediatric research (UNITED STATES) May **1999**, 45 (5 Pt 1) p635-42, ISSN 0031-3998 Journal Code: OWL
Contract/Grant No.: HL03267, HL, NHLBI; HL47670, HL, NHLBI; HL515333, HL, NHLBI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
During embryonic development the heart is required to grow in size and cell number, undergo complex morphologic alterations, and function to circulate the **blood** . Between embryonic d 10.5 (E10.5) and E11.5, cardiac myocytes undergo rapid cell division, resulting in doubling of cardiac mass, while metabolic requirements are increased and contraction force is enhanced. Accelerated cardiomyocyte differentiation is accompanied by a significant increase in trabeculation of ventricular myocardium. Many single **gene** mutations in the mouse result in a "thinned myocardium" and embryonic lethality between E10.5 and E13.5 secondary to heart failure. This is the case in the Splotch mouse in which a mutation of the Pax3 **gene** results in neural crest and cardiac defects. Nevertheless, the molecular events governing these important developmental steps remain largely unknown. Here, we describe the use of suppression subtractive hybridization to identify mRNA transcripts whose expression is enhanced during this critical period in normal hearts. These **genes** encode functions related to maturation of the contractile apparatus, cardiomyocyte differentiation, altered cellular metabolism, and transcriptional regulation. One of the **genes** that we identified, p57Kip2, encodes a cyclin-dependent kinase **inhibitor** of the **p21** family. We show that p57Kip2 is normally expressed in the inner trabecular layer of the developing heart. In Splotch embryos, expression of p57Kip2 is **expanded** to encompass the entire thickness of the myocardium. This result and further structural analysis suggests that the myocardial defect of Splotch embryos is associated with precocious cardiomyocyte differentiation.
? ds

Set	Items	Description
S1	7259	P21 AND (INHIBIT?)
S2	5082	S1 AND PY<2000
S3	65	S2 AND PLANT?
S4	61	RD (unique items)
S5	1	S4 AND TRANSGENIC?
S6	5017	S2 NOT S3
S7	54	S6 AND TRANSGENIC?
S8	38	RD (unique items)
S9	4963	S6 NOT S7
S10	73	S9 AND STEM?
S11	351	S9 AND BLOOD?
S12	410	S10 OR S11

S13 371 RD (unique items)
S14 221 S13 AND GEN
S15 2 S14 AND EXPAND?
? s s14 and p27

221 S14
4533 P27
S16 27 S14 AND P27
? t s16/3,ab/all

16/3,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10386000 20022676 PMID: 10555750
CDK-**inhibitor** independent cell cycle progression in an experimental haematopoietic **stem** cell leukaemia despite unaltered Rb-phosphorylation.
Huss R; Theis S; Deeg HJ
Institute of Pathology, University of Munich, Germany.
British journal of cancer (SCOTLAND) Nov **1999**, 81 (5) p808-13, ISSN 0007-0920 Journal Code: AV4
Contract/Grant No.: CA 18029, CA, NCI; CA 18221, CA, NCI; CA 31787, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
A CD34-negative haematopoietic progenitor cell line, D064, derived from canine bone marrow stromal cells is able to differentiate into haematopoietic progenitors under the influence of growth factor-mediated signalling. While differentiating, these cells eventually start to express MHC class II molecules (DR homologues) on their surface. The stable transfection of the fibroblast-like wild-type cells with retroviral constructs containing the cDNA for the canine MHC class II DR-**genes** (DRA and DRB) induces a change in morphology, accelerates cell cycle progression and leads to a loss of anchorage-dependent growth. Transfected cells show features of an immature **stem** cell leukaemia, such as giant cell formation. In wild-type D064 cells the accumulation of the cyclin-dependent kinase **inhibitor** (cdki) p27kip-1 induces differentiation, which is dependent upon signalling via the ligand for the tyrosine kinase receptor c-kit (**stem** cell factor). DR-transfected cells instead apparently grow independently of any growth factor-mediated signals and express high levels of the cdkis p27kip-1 and especially **p21**(waf-1/cip-1), concurrently with accelated cell cycle progression. In contrast to the overexpression of cdkis and despite accelerated cell cycle progression, the expression of the G2/M phase transition kinase p34cdc2 is significantly reduced in DR-transfected and transformed cells as compared to the haematopoietic wild-type cell line D064. This might suggest a possible alternative cell cycle progression pathway in this experimental **stem** cell leukaemia by by-passing the G0/G1 phase arrest, although retinoblastoma (Rb)-phosphorylation remains unaltered. These results provide evidence that mechanisms normally controlling the cell cycle and early haematopoietic differentiation are disrupted by the constitutive transcription and expression of MHC class II **genes** (DR) leading to a progression and growth of this experimental **stem** cell leukaemia independent from cell cycle controlling regulators such as **p27** and **p21**.

16/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10373475 99455018 PMID: 10523650
p57(Kip2) stabilizes the MyoD protein by **inhibiting** cyclin E-Cdk2 kinase activity in growing myoblasts.

Reynaud EG; Pelpel K; Guillier M; Leibovitch MP; Leibovitch SA
Laboratoire de Genetique Oncologique UMR 1599 CNRS, Institut Gustave Roussy, 94805 Villejuif, France.
Molecular and cellular biology (UNITED STATES) Nov **1999**, 19 (11) p7621-9, ISSN 0270-7306 Journal Code: NGY
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

We show that expression of p57(Kip2), a potent tight-binding **inhibitor** of several G(1) cyclin-cyclin-dependent kinase (Cdk) complexes, increases markedly during C2C12 myoblast differentiation. We examined the effect of p57(Kip2) on the activity of the transcription factor MyoD. In transient transfection assays, transcriptional transactivation of the mouse muscle creatine kinase promoter by MyoD was enhanced by the Cdk **inhibitors**. In addition, p57(Kip2), **p21** (Cip1), and **p27**(Kip1) but not p16(Ink4a) induced an increased level of MyoD protein, and we show that MyoD, an unstable nuclear protein, was stabilized by p57(Kip2). Forced expression of p57(Kip2) correlated with hypophosphorylation of MyoD in C2C12 myoblasts. A dominant-negative Cdk2 mutant arrested cells at the G(1) phase transition and induced hypophosphorylation of MyoD. Furthermore, phosphorylation of MyoD by purified cyclin E-Cdk2 complexes was **inhibited** by p57(Kip2). In addition, the NH2 domain of p57(Kip2) necessary for **inhibition** of cyclin E-Cdk2 activity was sufficient to **inhibit** MyoD phosphorylation and to stabilize it, leading to its accumulation in proliferative myoblasts. Taken together, our data suggest that repression of cyclin E-Cdk2-mediated phosphorylation of MyoD by p57(Kip2) could play an important role in the accumulation of MyoD at the onset of myoblast differentiation.

16/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10161911 99290771 PMID: 10361114
Expression of **p21**(Cip1/Waf1/Sdi1) and **p27** (Kip1) cyclin-dependent kinase **inhibitors** during human hematopoiesis.
Taniguchi T; Endo H; Chikatsu N; Uchimaru K; Asano S; Fujita T; Nakahata T; Motokura T
Fourth Department of Internal Medicine, the Department of Pathology, the Branch Hospital, School of Medicine, Tokyo, Japan.
Blood (UNITED STATES) Jun 15 **1999**, 93 (12) p4167-78, ISSN 0006-4971 Journal Code: A8G
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Expression of **p21** and **p27** cyclin-dependent kinase **inhibitors** is associated with induced differentiation and cell-cycle arrest in some hematopoietic cell lines. However, it is not clear how these **inhibitors** are expressed during normal hematopoiesis. We examined various human hematopoietic colonies derived from cord **blood** CD34(+) cells, bone marrow, and peripheral **blood** cells using a quantitative reverse transcription-polymerase chain reaction assay, immunochemistry, and/or Western blot analysis. **p21** mRNA was expressed increasingly over time in all of the colonies examined (granulocytes, macrophages, megakaryocytes, and erythroblasts), whereas **p27** mRNA levels remained low, except for erythroid bursts. Erythroid bursts expressed both **p21** and **p27** mRNAs with differentiation but expressed neither protein, whereas both proteins were expressed in megakaryocytes and peripheral **blood** monocytes. In bone marrow, **p21** was immunostained almost exclusively in a subset of megakaryocytes and **p27** protein was present in megakaryocytes, plasma cells, and endothelial cells. In megakaryocytes, reciprocal expression of **p27** to Ki-67 was evident and an inverse relationship between **p21** and Ki-67 positivities was also present, albeit less obvious. These observations suggest that a complex

lineage-specific regulation is involved in **p21** and **p27** expression and that these **inhibitors** are involved in cell-cycle exit in megakaryocytes.

16/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10114942 99233652 PMID: 10216085
Subcellular and cell-cycle expression profiles of CDK-**inhibitors** in normal differentiating myeloid cells.
Yaroslavskiy B; Watkins S; Donnenberg AD; Patton TJ; Steinman RA
Departments of Medicine and Cell Biology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA.
Blood (UNITED STATES) May 1 **1999**, 93 (9) p2907-17, ISSN 0006-4971 Journal Code: A8G
Contract/Grant No.: HL54172-01, HL, NHLBI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
A central question in hematopoiesis is how cell-cycling behavior changes during the emergence of the differentiated state. To further understand what **genetic** regulators might couple proliferation status to differentiation, we studied the expression of the cell-cycle **inhibitors** **p21** and **p27** during the in vitro differentiation of normal CD34(+) blast cells along the myeloid lineage. We find **p27** but not **p21** to be expressed in freshly harvested resting CD34(+) cells. Thereafter, **p21** levels peak concurrent with cellular proliferation and then decline in expression as cells undergo terminal differentiation. In contrast, **p27** levels are fairly constant but the subcellular localization of **p27** changes from nuclear expression to predominantly cytoplasmic expression and finally to perinuclear localization at progressive stages of differentiation. This report discusses the implications of these findings.

16/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09936872 99025939 PMID: 9808559
Growth and differentiation of human **stem** cell factor/erythropoietin-dependent erythroid progenitor cells in vitro.
Panzenbock B; Bartunek P; Mapara MY; Zenke M
Max-Delbruck-Centre for Molecular Medicine, MDC, Berlin, Germany; and the Humboldt University Berlin, Virchow Klinikum, Robert-Rossle-Klinik, Berlin, Germany.
Blood (UNITED STATES) Nov 15 **1998**, 92 (10) p3658-68, ISSN 0006-4971 Journal Code: A8G
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Stem cell factor (SCF) and erythropoietin (Epo) effectively support erythroid cell development in vivo and in vitro. We have studied here an SCF/Epo-dependent erythroid progenitor cell from cord **blood** that can be efficiently amplified in liquid culture to large cell numbers in the presence of SCF, Epo, insulin-like growth factor-1 (IGF-1), dexamethasone, and estrogen. Additionally, by changing the culture conditions and by administration of Epo plus insulin, such progenitor cells effectively undergo terminal differentiation in culture and thereby faithfully recapitulate erythroid cell differentiation in vitro. This SCF/Epo-dependent erythroid progenitor is also present in CD34(+) peripheral **blood** **stem** cells and human bone marrow and can be isolated, amplified, and differentiated in vitro under the same conditions. Thus, highly homogenous populations of SCF/Epo-dependent erythroid progenitors can be obtained in large cell numbers that are most suitable

for further biochemical and molecular studies. We demonstrate that such cells express the recently identified adapter protein p[redacted]dok) that is involved in signaling downstream of the c-kit/SCF receptor. Additionally, cells express the cyclin-dependent kinase (CDK) **inhibitors p21** (cip1) and **p27** (kip1) that are highly induced when cells differentiate. Thus, the in vitro system described allows the study of molecules and signaling pathways involved in proliferation or differentiation of human erythroid cells.

16/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09908156 98384274 PMID: 9716736
p21(cip1) rescues human mesenchymal **stem** cells from apoptosis induced by low-density culture.
van den Bos C; Silverstetter S; Murphy M; Connolly T
Osiris Therapeutics Inc., 2001 Aliceanna St., Baltimore, Md. 21231, USA. cvandenbos@osiristx.com
Cell and tissue research (GERMANY) Sep **1998**, 293 (3) p463-70, ISSN 0302-766X Journal Code: CQD
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Mammalian cells are programmed to undergo programmed cell death in response to a variety of conditions. We demonstrate that human mesenchymal **stem** cells (hMSCs) undergo programmed cell death upon seeding at low density. Under these conditions, we observed an increased proportion of cells in S-phase and a decreased proportion of cells in G1-phase. This indicated that a change in control of G1-S-phase transition in response to low-density seeding had occurred and, therefore, we measured the level of cyclin-dependent kinase **inhibitory** proteins governing this transition. Human MSCs cultured at low density exhibited lowered levels of both the **p21** and **p27** cyclin-dependent kinase **inhibitors**, and these protein levels appear to be regulated at a post-transcriptional level. Conversely, overexpression of the **p21** cell cycle-dependent kinase **inhibitor** but not that of **p27** protected hMSCs from programmed cell death upon culture at low density. Furthermore, **p21** and **p27** are expressed differentially during endochondrial bone development. The loss of **p21** in hypertrophic chondrocytes correlates with the onset of apoptosis during endochondrial ossification. We suggest that **p21** and **p27** play a central role in skeletal development.

16/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09803770 98314835 PMID: 9652727
Growth arrest associated with 12-o-tetradecanoylphorbol-13-acetate-induced hematopoietic differentiation with a defective retinoblastoma tumor suppressor-mediated pathway.
Uchimaru K; Taniguchi T; Yoshikawa M; Fujinuma H; Fujita T; Motokura T
Fourth Department of Internal Medicine, University of Tokyo, School of Medicine, Japan.
Leukemia research (ENGLAND) May **1998**, 22 (5) p413-20, ISSN 0145-2126 Journal Code: K9M
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The retinoblastoma tumor suppressor (Rb) **gene** product plays an essential role in cell-cycle regulation. However, its role in terminal differentiation of hematopoietic cells is speculative. Here we show a model of 12-o-tetradecanoylphorbol-13-acetate (TPA)-induced hematopoietic differentiation and growth arrest with a defective Rb-mediated pathway. TPA treatment arrested the cell cycle of a human hematopoietic cell line,

MEG-01s, at the G1-S boundary and induced expression of **p21** /SDI1/WAF1/CIP1 and **p27**/[redacted]. Both of these proteins were present in cyclin E-associated complexes, the histone H1 and Rb kinase activities of which were then inactivated. However, MEG-01s cells lacked the intact Rb protein and the Rb-mediated pathway was defective. This model raises a question about the role for Rb in terminal differentiation of hematopoietic cells.

16/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09449506 98033338 PMID: 9364045
Cyclin dependent kinase **inhibitors** and dominant negative cyclin dependent kinase 4 and 6 promote survival of NGF-deprived sympathetic neurons.
Park DS; Levine B; Ferrari G; Greene LA
Department of Pathology and Center for Neurobiology and Behavior, Columbia University College of Physicians and Surgeons, New York, New York 10032, USA.
Journal of neuroscience (UNITED STATES) Dec 1 **1997**, 17 (23) p8975-83, ISSN 0270-6474 Journal Code: JDF
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Neuronal apoptosis plays a critical role in both normal development and disease. However, the precise molecular events controlling neuronal apoptosis are not well understood. Previously, we hypothesized that cell cycle regulatory molecules function in controlling the apoptotic pathways of trophic factor-deprived neurons. To test this hypothesis, we used the RNA alphavirus Sindbis to express three known cyclin dependent kinase **inhibitors** (CKIs), p16(ink4), **p21**(waf/cip), and **p27** (kip1), and dominant negative mutant forms of four known G1 cyclin dependent kinases (CDKs), Cdk2, Cdk3, Cdk4, and Cdk6, in primary cultured rat superior cervical ganglion sympathetic neurons. We demonstrate that expression of each of the CKIs protects the postmitotic cultured neurons from apoptotic death evoked by withdrawal of NGF. In addition, we show that expression of dominant negative forms of Cdk4 or Cdk6, but not Cdk2 or Cdk3, protects NGF-deprived sympathetic neurons from death. Such findings suggest the participation of several CDKs and their cognate cyclins in a neuronal apoptotic pathway.

16/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08909526 96028506 PMID: 7549904
Role of p53 in leukemogenesis of chronic myeloid leukemia.
Lanza F; Bi S
Institute of Hematology, University of Ferrara, Italy.
Stem cells (UNITED STATES) Jul **1995**, 13 (4) p445-52, ISSN 1066-5099 Journal Code: BN2
Languages: ENGLISH
Document type: Journal Article; Review; Review, Tutorial
Record type: Completed
This review attempts to provide current information on the role played by the p53 **gene** in normal and leukemic hematopoiesis with particular emphasis on chronic myeloid leukemia. On the basis of the currently available data we can argue that p53 acts as a negative regulator of proliferation of myeloid mature cells and CD34+ progenitors, and its action is mediated through changes in cell cycle kinetics, mainly before the S phase. The p53-dependent pathway is also regulated by several proteins, including p16, **p21**, **p27** (cyclin-dependent kinase [CDK] **inhibitors**), and a few oncogenes (bcl-2, bax, MDM-2). Although there is some information about the changes in the p53 **gene** seen in various

types of leukemia, the functions and biological importance of these changes in the pathogenesis of leukemia are still largely elusive. During the past several years, accumulated evidence suggests that changes in the p53 **gene** are commonly associated with blast crisis of chronic myeloid leukemia (CML) but rarely with chronic phase, and they are represented by rearrangements, deletions and point mutations. As for most of the tumors, the majority of point mutations occur between exons 4 and 8 (hot regions). In patients with CML in blastic crisis the most frequent mechanism of p53 inactivation is complete deletion of one allele in association with a point mutation in the remaining allele. (ABSTRACT TRUNCATED AT 250 WORDS)

16/3,AB/10 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11981487 BIOSIS NO.: 199900234800
Induced differentiation of U937 cells by 1,25-dihydroxyvitamin D3 involves cell cycle arrest in G1 that is preceded by a transient proliferative burst and an increase in cyclin expression.
AUTHOR: Rots Nynke Y; Iavarone Antonio; Bromleigh Virginia; Freedman Leonard P(a)
AUTHOR ADDRESS: (a)Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY, 10021**USA
JOURNAL: Blood 93 (8):p2721-2729 April 15, **1999**
ISSN: 0006-4971
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The hormonal form of vitamin D, 1,25-dihydroxyvitamin D3 (1,25(OH)2D3), is a potent **inhibitor** of cellular proliferation as well as an inducer of differentiation of myeloid leukemic cells to macrophages. We have previously reported that a number of **genes** are upregulated by 1,25(OH)2D3 during myeloid differentiation, including the cyclin-dependent kinase (CDK) **inhibitors p21**, **p27**, 15, and p18, suggesting that cell cycle arrest and differentiation are tightly linked processes. We further explore here the relationship between growth **inhibition** and differentiation. We report that, upon 1,25(OH)2D3 treatment, U937 cells exhibited an early proliferative burst followed by growth **inhibition** and subsequent differentiation. Although CDK levels remain constant throughout, this transient increase in proliferation was accompanied by increases in cyclin A, D1, and E protein levels. **p21** and **p27** levels were also elevated during both the proliferative burst and subsequent **inhibition** of cell growth. Ectopic overexpression of **p21** and/or **p27** in U937 cells, in the absence of hormone, resulted in an induction of the expression of monocyte/macrophage-specific markers, whereas overexpression of p15 and p18 had no effect, suggesting that a subset of CDK **inhibitors** are important for both growth arrest and differentiation and that an early increase in proliferation is somehow a prerequisite for subsequent differentiation. However, no such biphasic behavior was detected in cells that are growth **inhibited** by 1,25(OH)2D3 but do not differentiate, such as MCF-7 cells. Taken together, these results indicate that both growth stimulation and subsequent **inhibition** precede differentiation and involve induction of both cyclins and **p21** and **p27**, whereas cell cycle arrest of differentiated cells can be achieved simply by elevations in CDK **inhibitors**.

1999

16/3,AB/11 (Item 2 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)
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11802465 BIOSIS NO.: 199900048574
Expression of cell cycle regulatory **genes** in chronic myelogenous leukemia.
AUTHOR: Iolascon Achille(a); Della Ragione Fulvio; Giordani Lucia; Serra Anan; Saglio Giuseppe; Faienza Maria Felicia
AUTHOR ADDRESS: (a)Dep. Biomedical Eta Evolutiva, Piazza G. Cesare 11, 70134 Bari**Italy
JOURNAL: Haematologica 83 (9):p771-777 Sept., **1998**
ISSN: 0390-6078
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background and Objective. Cell cycle regulatory **genes** are frequently altered In a variety of malignancies. The structure and pattern of expression of eight **genes** Involved In cell division cycle control were studied In leukemic cell samples prepared from bone marrow of patients affected by chronic myelogenous leukemia. Design and Methods. Ten cell preparations were obtained from patients In the chronic phase, five from those In myeloid blast crisis and five from those In the lymphoid acute phase. Moreover, bone marrow CD34+ cells, purified from healthy subjects and patients with chronic myelogenous leukemia (both during chronic and acute phases), were analyzed. The Investigated **genes** were RB1, p53 and six cyclin-dependent kinase **Inhibitor genes** (p15INK4B, p16INK4A, p18INK4C, p21WAF1/CIP1, p27KIP1, P57KIp2). Results. We found that none of these **genes** Is structurally altered In either the chronic or acute phases, with the single exception of the p16INK4A **gene**, which was homozygously deleted In 1 case of lymphoid evolution. p57Kip2 expression Is down-regulated during the evolution towards the blast crisis both In malignant and CD34+ cells. In addition, a significant up-regulation of p15INK48 **gene** expression is observable during the development of the acute phase of malignancy. Interpretations and Conclusions. The transcriptional modulation of some cyclin-dependent kinase **Inhibitors** might contribute to the fatal blast crisis of chronic myelogenous leukemia.

1998

16/3,AB/12 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11685599 BIOSIS NO.: 199800467330
Lineage-associated expression of cyclin-dependent kinase-**inhibitors** during hematopoietic differentiation.
AUTHOR: Teofili L; Larocca L M; Chiusolo P; Martini M; Maggiano N; Morosetti R; Leone G
AUTHOR ADDRESS: Dep. Hematology, Catholic Univ., Rome**Italy
JOURNAL: Experimental Hematology (Charlottesville) 26 (8):p717 Aug., **1998**
CONFERENCE/MEETING: 27th Annual Meeting of the International Society for Experimental Hematology Vancouver, British Columbia, Canada August 1-5, 1998
SPONSOR: International Society for Experimental Hematology
ISSN: 0301-472X
RECORD TYPE: Citation
LANGUAGE: English
1998

16/3,AB/13 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11652356 BIOSIS NO.: 199800434087
Involvement of the Ink4 proteins np16 and p15 in T-lymphocyte senescence.
AUTHOR: Erickson Sven; Sangfelt Olle; Heyman Mats; Castro Juan; Einhorn Stefan; Grander Dan(a)
AUTHOR ADDRESS: (a)Dep. Oncol. Pathol., Karolinska Hosp. Inst., S-171 76 Stockholm**Sweden
JOURNAL: Oncogene 17 (5):p595-602 Aug. 6, **1998**
ISSN: 0950-9232
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Little is known about the molecular background to senescence in T-lymphocytes. In fibroblast systems replicative senescence has been shown to correlate with a number of changes in the expression of the proteins normally regulating progression through the G1 phase of the cell cycle, and recently the Ink4 **inhibitor** p16 was implicated as a central regulator of replicative senescence in human fibroblasts. It has, however, been claimed that p16 is not expressed in T-lymphocytes. In the present study we have analysed G1 regulating proteins in ageing human T-lymphocytes. We show that PHA-and IL-2 stimulated T-lymphocytes cease to proliferate after around 20 population doublings, these cells can not thereafter be restimulated to growth, and were also found to exhibit markers for senescence. We found that T-lymphocytes accumulate p16 and p15 protein during successive population doublings and display high levels of these proteins as they enter into replicative senescence. There was also an increased binding of p16 to the Cdk6 kinase in senescent cells, and a decreased Cdk6 as well as Cdk2 kinase activity. The levels of other G1 regulating proteins were also altered in the senescent cells, such as slightly elevated levels of **p21**/WAF1, and downregulation of Cdk2 and cyclinD3. The levels of **p27**/Kip1 is down regulated in proliferating cells but rise to approximately 15% of the levels in un-stimulated quiescent cells. As a high proportion of T-cell childhood acute lymphoblastic leukaemias have deletions of both p15 and p16, our data suggest that inactivation of these **genes** makes it possible for leukemic cells to avoid senescence.

1998

16/3,AB/14 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11181068 BIOSIS NO.: 199799802213
Molecular analysis of cyclin-dependent kinase **inhibitors** in human leukemias.
AUTHOR: Hayette S; Thomas X; Bertrand Y; Tigaud I; Callanah M; Thiebaut A; Charrin C; Archimbaud E; Magaudi J-P; Rimokh R
AUTHOR ADDRESS: INSERM Unite 453, Cent. Leon Berard, 28 rue Laennec, 69373 Lyon Cedex 08**France
JOURNAL: Leukemia (Basingstoke) 11 (10):p1696-1699 **1997**
ISSN: 0887-6924
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Recurrent anomalies of the short arm of chromosome 9, including interstitial deletions and translocations, have often been described. Recently two cyclin-dependent kinase **inhibitors**, known as P16 (INK4A/MTS1) and P15 (INK4B/MTS2), which map to 9p21, have been found deleted in a wide range of tumors and particularly in leukemic cells. We

report here Southern blot analyses of cyclin-dependent kinase **inhibitors** (P16, P15, **P21** and **P27**) status in primary tumoral cells of 121 patients with acute lymphoblastic leukemias, 85 patients with acute myeloid leukemias and 42 patients with B-chronic lymphocytic leukemias. P16 inactivation was found in 25 of 38 T-ALLs and in 28 of 83 B-lineage ALLs. In eight cases (three T-ALLs and five B-lineage ALLs), one or both alleles of P16 locus were rearranged. In these cases, breakpoints occurred within the two major breakpoints cluster regions previously described in T-ALLs. Homozygous P16 deletions were observed in two of 85 AMLs but in none of the 42 B-CLL cases tested. Our results suggest that P16 inactivation are the most frequent event observed in ALL (44%), are quite rare in AML (lt 2%) and seem to be absent in CLL. Search for **P27** and **P21** deletion was negative in B/T-lineage ALLs and monoallelic deletions of **P27** were found in four AML cases (5%).

1997

16/3,AB/15 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11117633 BIOSIS NO.: 199799738778
G1 arrest and high expression of cyclin kinase and apoptosis **inhibitors** in accumulated activated/memory phenotype CD4+ cells of older lupus mice.
AUTHOR: Sabzevari Helen; Propp Stephanie; Kono Dwight H; Theofilopoulos Argyrios N(a)
AUTHOR ADDRESS: (a)Immunol. Dep., Scripps Res. Inst., 10550 N. Torrey Pines Rd./IMM3, La Jolla, CA 92037**USA
JOURNAL: European Journal of Immunology 27 (8):p1901-1910 **1997**
ISSN: 0014-2980
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A **general** characteristic of lupus-prone mice (and humans) is the expedited accumulation of large numbers of presumably self-reactive activated/memory phenotype T cells. The mechanism by which these cells escape apoptosis has not been defined. We used activated/memory phenotype CD4+ cells from male BXSB mice with early-life severe lupus-like disease to investigate cell cycle status and apoptosis susceptibility, and to determine the role of corresponding **genes** in survival of these cells. In vitro acridine orange staining indicated that most of the rapidly accumulating memory phenotype CD4+ T cells of 4-month-old male BXSB mice are G1 arrested. Long-term bromodeoxyuridine in vivo labeling also showed that with advanced age, there was a shift of the CD4+ CD44-hi male cells from predominantly cycling to predominantly noncycling. Moreover, the CD4+ CD44-hi cells of older males were refractory to anti-CD3-induced proliferation and apoptosis. Using a multiprobe RNase protection assay encompassing riboprobe panels for cell cycle and apoptosis-related **genes**, we found that these cells exhibited high expression of certain members of the Ink4 (p18-Ink4C) and Cip/Kip (**p21**-Cip1) families of cyclin kinase **inhibitors** as well as of the apoptosis-**inhibiting** BCl-x-L **gene**. Western blot analysis confirmed increased levels of BCl-x-L and **p21**-Cip1, and also identified increases in another cyclin kinase **inhibitor**, **p27**-Kip1. We propose that in autoimmunity, self-reactive CD4+ cells are subjected to successive rounds of activation/division that eventually lead to a build-up in cyclin-dependent kinase **inhibitors**. Once high levels of such **inhibitors** are reached, they cause refractoriness to further activation, impaired cell cycle entry and resistance to apoptosis, a situation akin to replicative senescence.

1997

16/3,AB/16 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10922440 BIOSIS NO.: 199799543585
Thrombopoietin-induced differentiation of a human megakaryoblastic leukemia cell line, CMK, involves transcriptional activation of **p21** -WAF1/Cip1 by STAT5.
AUTHOR: Matsumura Itaru; Ishikawa Jun; Nakajima Koichi; Oritani Kenji; Tomiyama Yoshiaki; Miyagawa Jun-Ichiro; Kato Takashi; Miyazaki Hiroshi; Matsuzawa Yuji; Kanakura Yuzuru(a)
AUTHOR ADDRESS: (a)Dep. Hematol. Oncol., Osaka Univ. Med. Sch., 2-2 Yamadaoka, Suita, Osaka 565**Japan
JOURNAL: Molecular and Cellular Biology 17 (5):p2933-2943 **1997**
ISSN: 0270-7306
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Although thrombopoietin (TPO) is known to play a fundamental role in both megakaryopoiesis and thrombopoiesis, the molecular mechanism of TPO-induced megakaryocytic differentiation is not known. In a human megakaryoblastic leukemia cell line, CMK, that showed some degree of megakaryocytic differentiation after culture with TPO, the cyclin-dependent kinase (Cdk) **inhibitor p21**-WAF1/Cip1, but not **p27**-Kip1, p16-INK4A, p15-INK4B, or p18-INK4C, was found to be upregulated in an immediately early response to TPO. The expression of **p21** was found to be sustained over a period of 5 days by treatment with TPO in large polyploid cells that developed in response to TPO, but not in small undifferentiated cells, indicating a close correlation between the ligand-induced differentiation and **p21** induction in CMK cells. To examine potential roles of Cdk **inhibitors** in megakaryocytic differentiation, CMK cells were transfected with the **p21**, **p27**, or p16 **gene**, together with a marker **gene**, beta-galactosidase, and were cultured with medium alone for 5 days. The ectopic expression of **p21** or **p27** but not of p16 led to induction of megakaryocytic differentiation of CMK cells. Overexpression of the N-terminal domain (amino acids (aa) 1 to 75) of **p21** was sufficient to induce megakaryocytic differentiation, whereas that of the C-terminal domain (aa 76 to 164) had little or no effect on morphological features. Furthermore, we found that although TPO induced tyrosine phosphorylation of both STAT3 and STAT5 in CMK cells, only STAT5 showed binding activities to potential STAT-binding sites that locate in the promoter region of **p21 gene** (**p21**-SIE sites), thereby leading to transactivation of **p21**. These results suggested that **p21** induction, possibly mediated through activated STAT5, could play an important role in TPO-induced megakaryocytic differentiation.

1997

16/3,AB/17 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10745929 BIOSIS NO.: 199799367074
Alterations of the cyclin-dependent kinase **inhibitor** p19-INK4D is rare in hematopoietic malignancies.
AUTHOR: Shiohara M; Spirin K; Said J W; Gombart A F; Nakamaki T; Takeuchi S ; Hatta Y; Morosetti R; Tasaka T; Seriu T; Bartram C; Miller C W; Tomonaga M; Koeffler H P(a)
AUTHOR ADDRESS: (a)Div. Hematology/Oncology, Cedars-Sinai Res. Inst./UCLA Sch. Med., 8700 Beverly Blvd., B213, Los **USA

JOURNAL: Leukemia (Basingstoke) 10 (12):p1897-1900 **1996**
ISSN: 0887-6924
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Cyclin-dependent kinase **inhibitors** (CDKIs) can be classified into two groups based on the structure of the proteins. One group includes the **p21** (CIP1, WAF1, CAP20), **p27** (Kip1), and p57 (Kip2) CDKIs, which contain a homologous amino-terminal cyclin-dependent kinase (cdk) **inhibitory** domain. The p16 (INK4A), p15 (INK4B), and p1B (INK4C) CDKIs, which have an ankyrin repeat motifs, belong to the other group. The p16 and p15 CDKI **genes** are very frequently altered in a variety of cancers including hematopoietic malignancies. The pig (INK4D) **gene** is a newly cloned CDKI which belongs to the latter group. To determine if pig **genetic** alterations play a role in hematopoietic malignancies, we examined DNA from 45 childhood newly diagnosed acute lymphocytic leukemias (ALLs), 30 acute myeloblastic leukemias (AMLs), 10 chronic myelocytic leukemias (CMLs), 45 adult T cell leukemias (ATLs), 70 non-Hodgkin's lymphomas (NHLs), and 20 multiple myelomas (MM) as well as 14 ALL, 20 AML, two ATL, and five lymphoma cell lines. Using Southern blot analysis, one homozygous deletion of the pig **gene** was detected in a human immunodeficiency virus (HIV)-related Burkitt-like lymphoma sample. No point mutations in any of the samples were found by polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP) analysis. Our investigation suggests that alterations of p19 do not play an important role in the development of most hematopoietic malignancies.

1996

16/3,AB/18 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10732571 BIOSIS NO.: 199799353716
Sensitive quantification of human cyclin-dependent kinase **inhibitor** (CKI) expression by competitive RT-PCR suitable for the analysis of small biopsy samples from human tumours.
AUTHOR: Schwaller J; Pabst T; Bickel M; Fey M F; Tobler A
AUTHOR ADDRESS: University Inselspital, Berne**Switzerland
JOURNAL: Blood 88 (10 SUPPL. 1 PART 1-2):p384A **1996**
CONFERENCE/MEETING: Thirty-eighth Annual Meeting of the American Society of Hematology Orlando, Florida, USA December 6-10, 1996
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English
1996

16/3,AB/19 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10732185 BIOSIS NO.: 199799353330
Regulation of CDK2 activity in polyploid megakaryocytes by the CDK-**inhibitory** proteins **P21**-CIP1 and **P27**-KIP1.
AUTHOR: Datta N S; Long M W
AUTHOR ADDRESS: Dep. Pediatrics, Univ. Michigan, Ann Arbor, MI**USA
JOURNAL: Blood 88 (10 SUPPL. 1 PART 1-2):p287A **1996**
CONFERENCE/MEETING: Thirty-eighth Annual Meeting of the American Society of Hematology Orlando, Florida, USA December 6-10, 1996
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English

16/3,AB/20 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10664788 BIOSIS NO.: 199799285933
Involvement of **p21**-cip-1 and **p27**-kip-1 in the molecular mechanisms of steel factor-induced proliferative synergy in vitro and of **p21**-cip-1 in the maintenance of **stem**/progenitor cells in vivo.
AUTHOR: Mantel Charlie; Luo Zaiming; Canfield Jeff; Braun Steve; Deng Chuxia; Broxmeyer Hal E(a)
AUTHOR ADDRESS: (a)Walther Oncol. Cent., Indiana Univ. Sch. Med., 975 W Walnut St., Room 501, Indianapolis, IN 4620**USA
JOURNAL: Blood 88 (10):p3710-3719 **1996**
ISSN: 0006-4971
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Steel factor (SLF) is a hematopoietic cytokine that synergizes with other growth factors to induce a greatly enhanced proliferative state of hematopoietic progenitor cells and factor-dependent cell lines. Even though the in vivo importance of SLF in the maintenance and responsiveness of **stem** and progenitor cells is well documented, the molecular mechanisms involved in its synergistic effects are mainly unknown. Some factor-dependent myeloid cell lines respond to the synergistic proliferative effects of SLF plus other cytokines in a manner similar to that of normal myeloid progenitor cells from bone marrow and cord **blood**. We show here that SLF can synergize with granulocyte-macrophage colony-stimulating factor (GM-CSF) to induce an enhanced phosphorylation of the retinoblastoma **gene** product and a synergistic increase in the total intracellular protein level of the cyclin-dependent kinase **inhibitor**, **p21**-cip-1, which is correlated with a simultaneous decrease in **p27**-kip-1 in the human factor-dependent myeloid cell line, M07e. Moreover, these cytokines synergize to increase **p21**-cip-1 binding and decrease **p27**-kip-1 binding to cyclin-dependent kinase-2 (cdk2), an enzyme required for normal cell cycle progression; these inverse events correlated with increased cdk2 kinase activity. It is also shown that exogenous purified **p21**-cip-1 can displace **p27**-kip-1 already bound to cdk2 in vitro. These data implicate increased **p21**-cip-1 and decreased **p27**-kip-1 intracellular concentrations and their stoichiometric interplay in the enhanced proliferative status of cells stimulated by the combination of SLF and GM-CSF. In support of these findings, it is shown that hematopoietic progenitor cells from mice lacking **p21**-cip-1 are defective in SLF synergistic proliferative response in vitro. Moreover, the cycling status of marrow and spleen progenitors and absolute numbers of marrow progenitors were significantly decreased in the **p21**-cip-1 -/-, compared with the +/+ mice. We conclude that the cdk threshold regulators **p21**-kip-1 and **p27**-kip-1 play a critical role in the normal mitogenic response of M07e cells and murine myeloid progenitor cells to these cytokines and particularly in the SLF synergistic proliferative response that is important to the normal maintenance of the **stem**/progenitor cell compartment.

1996

16/3,AB/21 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10627887 BIOSIS NO.: 199699249032

A novel pre-B acute lymphoblastic leukemia cell line with chromosomal translocation between p[redacted]INK4-A/P-15INK4B tumor suppres[redacted] and immunoglobulin heavy chain **genes**: TGF-beta/IL-7 **inhibitory** signaling mechanism.

AUTHOR: Urashima M; Hoshi Y; Sugimoto Y; Kaihara C; Matsuzaki M; Chauhan D; Ogata A; Teoh G; Decaprio J A; Anderson K C(a)
AUTHOR ADDRESS: (a)Dana-Farber Cancer Inst., 44 Binney St., Boston, MA 02215**USA

JOURNAL: Leukemia (Basingstoke) 10 (10):p1576-1583 **1996**
ISSN: 0887-6924
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: p16-INK4A and/or p15-INK4B **genes** are frequently deleted in leukemias and other cancers. We have established a novel pre-B acute lymphoblastic leukemia (ALL) cell line (JKB2) with a chromosomal translocation between 9p21 and 14q32, on which p16-INK4A/p15-INK4B and heavy chain immunoglobulin (Ig) **genes**, respectively, are located. Homozygous deletions of P16-INK4A/p15-INK4B **genes** in JKB2 cells were confirmed by polymerase chain reaction, and their protein products were not detectable by Western blotting. Therefore JKB2 is the first example of an immunoglobulin heavy chain translocation associated with deletions of these **genes**. In JKB2 cells, cyclin-dependent kinase(CDK)4 and CDK6 formed complexes with cyclin D, due to the lack of p16, triggering phosphorylation of retinoblastoma protein (pRB) and continuous cell proliferation. Moreover, the growth of JKB2 cells was partially **inhibited** by TGF-beta or IL-7, accompanied by decreased CDK4 and CDK6 expression, increased **p21** and **p27** expression, decreased **p27** binding to CDK4/CDK6, and increased binding of **p27** to CDK2. In addition, IL-7 both **inhibited** proliferation and induced differentiation of JKB2 cells. These studies suggest that a t(9;14)(**p21**;q32) chromosomal translocation can result in deletion of both p16-INK4A and p15-INK4B **genes** in pre-B ALL, and that the JKB2 cell line therefore provides a model for the study of leukemogenesis related to abnormalities in chromosome 9p21. Moreover, they suggest that TGF-beta can suppress JKB2 cell growth in a p15-independent mechanism.

1996

16/3,AB/22 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10605337 BIOSIS NO.: 199699226482
Cyclin-dependent kinase **inhibitors** (CKIs) and hematological malignancies.

AUTHOR: Baghdassarian N; Ffrench M(a)
AUTHOR ADDRESS: (a)Lab. Central Hematologie Cytogenetique, Pav. E, Hopital Edouard Herriot, Place d'Arsonval, F-694**France

JOURNAL: Hematology and Cell Therapy 38 (4):p313-323 **1996**
ISSN: 1430-2772
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English; French

ABSTRACT: Cell proliferation control is ensured by a group of proteins named cyclin-dependent kinases (CDKs), the activation of which is dependent on phosphorylation and cyclin association. In parallel, these CDKs are negatively controlled by two distinct groups of **inhibitory** proteins, the cyclin-dependent kinase **inhibitors** (CKIs). The first group, including p16-Ink4a, p15-Ink4b, p18-Ink4c and p19-Ink4d, is specific for the G1 CDKs, CDK4 and CDK6, **inhibiting** the kinase

activity of cyclin D/CDK4, CDK6 complexes on pRb. p16-Ink4a down-regulated by pRb, **inhibits** G1 CDKs by competition with cyclin D; p15-Ink4b, the synthesis of which is induced by TGF-beta, seems to be a mediator of TGF-beta-mediated cell cycle arrest. Furthermore, p18-Ink4c **inhibits** CDK6 phosphorylation and activation by CAK. The second CKIs family is constituted by **p21**-Waf1, **p27**-Kip1 and p57-Kip2. Their **inhibitory** action concerns a large range of cyclin/CDK complexes involved in G1 and S phase. **p21**-Waf1, induced in part by p53, is up-regulated by senescence, DNA damage and cellular differentiation. **p21**-Waf1 forms quaternary complexes with CDKs, cyclins and PCNA. Its **inhibitory** action, preventing CDK from phosphorylation, depends on the stoichiometry of the components. As p15-Ink4b, **p27**-KiP1 causes late G-1 cell cycle arrest after TGF-beta treatment and contact **inhibition**. The implications of CKIs in hematological malignancies are function of deletions or mutations of their **genes**. p16-Ink4a and p15-Ink4b **genes**, localized on 9p21, present frequent homozygous deletions in ALL T, ATL and lymphoblastic acutisation of CML. The other CKIs present very rare homozygous deletions or mutations, particularly **p21**-Waf1 and **p27**-Kip2. However, reduction of **inhibitory** activity due to hemizygous deletions might favour leukemogenesis.

1996

16/3,AB/23 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10564333 BIOSIS NO.: 199699185478
Induction to cell cycle regulatory proteins in anti-immunoglobulin-stimulated mature B lymphocytes.
AUTHOR: Solvason Nanette; Wu Wei Wei; Kabra Nisha; Wu Xiaoyan; Lees Emma; Howard Maureen C(a)
AUTHOR ADDRESS: (a)Dep. Immunol., DNAX Res. Inst., 901 California Ave., Palo Alto, CA 94304-1104**USA
JOURNAL: Journal of Experimental Medicine 184 (2):p407-417 **1996**
ISSN: 0022-1007
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Progression through the cell cycle is a tightly controlled process that integrates signals **generated** at the plasma membrane with the proteins that form the cell cycle machinery. The current study chronicles the induction of cyclins, cyclin-dependent kinases (cdk), and cdk **inhibitors** in low density primary mouse B lymphocytes after anti-immunoglobulin plus interleukin 4 (IgM + IL-4) stimulation. In this system, 85% of cells remain in the G0/G1 phase of cell cycle for an initial 24-h period, followed by entry of up to 50% of the cells into S phase, commencing around 30 h and peaking at 48 h. Extensive time course analyses of these anti-IgM + IL-4-stimulated B cells revealed that the G1-associated D-type cyclins D2 and D3 were induced by 3 h after stimulation, and that cyclins E, A, and B were subsequently induced sequentially, beginning at mid-G1, G1/S transition, and S phase, respectively. The G1-associated cyclin D1 was not expressed at any stage of the anti-Ig + IL-4-induced B cell cycle. cdk2, cdk4, and cdk6 were induced during G1, whereas cell division cycle-2 (cdc2) was induced concomitantly with S phase. Irrespective of their expression, the kinases cdk2 and cdc2 were only active from S phase onwards, suggesting that productive cyclin/kinase complex formation did not occur until that time. Cell cycle **inhibitors p21** and p19 were induced by anti-Ig + IL-4, peaking in expression at mid-G1 and S phase, respectively. Stimulation of low density B cells with anti-Ig + IL-4 caused rapid down regulation of the **p27 inhibitor**, however this protein was

reexpressed at 54-96 h after stimulation. In contrast, B cells stimulated with anti-CD40, a stimulus which induces long-term B cell proliferation, permanently down regulated **p27**. These findings are consistent with the concept that **p27** reexpression contributes to the G1 arrest that follows antigen receptor crosslinking. Low density B cells cultured in the viability-enhancing cytokine IL-4 alone also showed induction of D2 and D3 cyclin expression. However, the D2 expression was transient, and the D3 expression was substantially lower than that observed in B cells induced to proliferate by anti-Ig + IL-4. This partial induction of D2 and D3 expression may explain IL-4's ability to promote B cell entry into G1 but not S phase of cell cycle, and furthermore, its ability to truncate G1 progression when B cells are subsequently stimulated with anti-Ig.

1996

16/3,AB/24 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10355384 BIOSIS NO.: 199698810302
The expression of TGF-beta-1 and the cyclin dependent kinase **inhibitors p27** and **p21** in MCF-7 breast epithelial cells in response to phorbol esters.
AUTHOR: Shuter E(a); Nutt J(a); Horne C H W; Lunec J(a)
AUTHOR ADDRESS: (a)Cancer Research Unit, Med. Sch., Newcastle upon Tyne NE2 4HH**UK
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 37 (0):p10 **1996**
CONFERENCE/MEETING: 87th Annual Meeting of the American Association for Cancer Research Washington, D.C., USA April 20-24, 1996
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
1996

16/3,AB/25 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10221530 BIOSIS NO.: 199698676448
Withdrawal of differentiation **inhibitory** activity/leukemia **inhibitory** factor up-regulates D-type cyclins and cyclin-dependent kinase **inhibitors** in mouse embryonic **stem** cells.
AUTHOR: Savatier P(a); Lapillonne H; Van Grunsven L A; Rudkin B B; Samarut J
AUTHOR ADDRESS: (a)Lab. Biol. Mol. Cell., UMR 49 CNRS, LA INRA, Ecole Normale Superieure Lyon, 46 allee d'Italie, 6**France
JOURNAL: Oncogene 12 (2):p309-322 **1996**
ISSN: 0950-9232
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The expression of E and D-type cyclins, Cyclin-Dependent Kinase (CDK) 2 and 4, as well as CDK **inhibitors p21**-Cip1 and **p27**-Kip1 were examined during in vitro differentiation of mouse embryonic **stem** (ES) cells. ES cells cultured in presence of Differentiation **Inhibitory** Activity/Leukemia **Inhibitory** Factor (DIA/LIF) express very low levels of cyclin E/CDK2 complexes, p21-Cip1 and **p27**-Kil11 CDK **inhibitors**, while cylin D/CDK4-associated kinase activity is undetectable. Withdrawal of DIA/LIF, which induces differentiation, results in the progressive up-regulation

of all. Up-regulation of D-cyclins occurs through an increase in the steady-state levels of mRNA concomitantly with the activation of Brachyury and Goosecoid, two early markers of mesoderm differentiation. Similarly, cells from the epiblast of the early postimplantation mouse embryo do not express any cyclin D/CDK4 complexes. These are progressively upregulated at gastrulation and early organogenesis. DIA/LIF-stimulated ES cells are not growth-arrested by overexpression of p16-Ink4a, a specific **inhibitor** of CDK4 and CDK6. We propose that the G1/S transition may be regulated by a minimal mechanism in mouse embryonic **stem** cells. Induction of differentiation triggers the establishment of a more sophisticated mechanism involving both cyclin D/CDK4- and CDK **inhibitor**-associated control of G1-phase progression.

1996

16/3,AB/26 (Item 17 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10221414 BIOSIS NO.: 199698676332
Isolation and characterization of p19-INK4d, a p16-related **inhibitor** specific to CDK6 and CDK4.
AUTHOR: Guan Kun-Liang; Jenkins Christopher W; Li Yan; O'Keefe Christine L; Noh Seong; Wu Xiaoyu; Zariwala Maimoona; Matera A Gregory; Xiong Yue(a)
AUTHOR ADDRESS: (a)Lineberger Comprehensive Cancer Cent., Univ. N.C. at Chapel Hill, Chapel Hill, NC 27599-3280**USA
JOURNAL: Molecular Biology of the Cell 7 (1):p57-70 **1996**
ISSN: 1059-1524
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Cyclin-dependent kinases 4 and 6 are complexed with many small cellular proteins in vivo. We have isolated cDNA sequences, INK4d, encoding a 19-kDa protein that is associated with CDK6 in several hematopoietic cell lines. p19 shares equal similarity and a common ancestor with other identified **inhibitors** of the p16/INK4 family. p19 interacts with and **inhibits** the activity of both CDK4 and CDK6 and exhibits no detectable interaction with the other known CDKs. p19 protein is present in both cell nuclei and cytoplasm. The p19 **gene** has been mapped to chromosome 19p13.2, and the level of its mRNA expression varies widely between different tissues. In contrast to **p21** and **p27** whose interaction with CDK subunits is dependent on or stimulated by the cyclin subunit, the interaction of p19 and p18 with CDK6 is hindered by the cyclin protein. Binary cyclin D1-p18/p19 or cyclin D1-CDK6 complexes are highly stable and cannot be dissociated by excess amounts of cyclin D1 or p19/p18 proteins, suggesting that p16 **inhibitors** and D cyclins may interact with CDKs 4 and 6 in a competing or potentially mutually exclusive manner.

1996

16/3,AB/27 (Item 18 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09767835 BIOSIS NO.: 199598222753
Assignment of the human **p27**-Kip1 **gene** to 12p13 and its analysis in leukemias.
AUTHOR: Pietenpol Jennifer A; Bohlander Stefan K; Sato Yuko; Papadopoulos Nickolas; Liu Bo; Friedman Cynthia; Trask Barbara J; Roberts James M; Kinzler Kenneth W; Rowley Janet D; Vogelstein Bert(a)

AUTHOR ADDRESS: (a)Johns Hopkins Oncol. Center, Molecular Genetics Lab., 424 North Bond St., Baltimore, MD 21231-10**USA
JOURNAL: Cancer Research 55 (6):p1206-1210 **1995**
ISSN: 0008-5472
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The **p27**-Kip1 (**p27**) **gene** encodes an inducible **inhibitor** of cyclin-dependent kinase activity. Using a murine **p27** cDNA as probe, we obtained a human cDNA clone and subsequently used it to isolate a genomic clone of this **gene**. The coding region of the human **p27 gene** was contained in two exons. Both the amino acid sequence and intron-exon organization of **p27** were similar to those previously found for the related cyclin-dependent kinase **inhibitor p21**-Waf1 (**p21**). The **p27 gene** was localized to chromosome band 12p13 by a combination of somatic cell hybrid and fluorescence in situ hybridization analyses. The **p27 gene** product is thought to control the leukocyte cell cycle and the 12p13 chromosomal band is known to be deleted in leukemias, suggesting that the **p27 gene** may act as a tumor suppressor **gene** in leukemias. Although **p27** was found to reside in the minimal region of chromosomal loss in hematological malignancies, no mutations of **p27** were observed in leukemia samples. Haploinsufficiency of **p27** may confer a growth advantage to leukemia cells.

1995
? s sp1 and p27 and (mouse or rat)

```
          9240  SP1
          4533  P27
        814214  MOUSE
       1669403  RAT
   S17       4  SP1 AND P27 AND (MOUSE OR RAT)
```
? s p21 and p27 and (mouse or rat)

```
         19427  P21
          4533  P27
        814214  MOUSE
       1669403  RAT
   S18     313  P21 AND P27 AND (MOUSE OR RAT)
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? s s18 and py<2001

Processing

```
           313  S18
      23736114  PY<2001
   S19     248  S18 AND PY<2001
```
? rd

...examined 50 records (50)
...examined 50 records (100)
...examined 50 records (150)
...examined 50 records (200)
...completed examining records

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   S20     192  RD (unique items)
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? t s20/3,ab/all

20/3,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11220570 21112346 PMID: 11170841
Indomethacin inhibits endothelial cell proliferation by suppressing cell cycle proteins and PRB phosphorylation: a key to its antiangiogenic action?
Pai R; Szabo IL; Kawanaka H; Soreghan BA; Jones MK; Tarnawski AS

Medical Service, Department of Veterans Affairs Medical Center, Long Beach, California 90822, [redacted]
Molecular cell biology research communications (United States) Aug **2000**, 4 (2) p111-6, ISSN 1522-4724 Journal Code: DRR
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit angiogenesis in vivo and in vitro, but the mechanism of this action is unclear. Angiogenesis-formation of new capillary vessels-requires endothelial proliferation, migration, and tube formation. It is stimulated by basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF). The cell cycle is regulated positively by cyclins and negatively by cyclin-dependent kinase inhibitors (CKI) and the retinoblastoma protein (pRb). Since the effects of NSAIDs on cell cycle-regulatory proteins in endothelial cells remain unknown, we examined the effect of indomethacin on bFGF-stimulated endothelial cell proliferation and on cell cycle regulatory proteins in **rat** primary aortic endothelial cells (RAEC). Indomethacin significantly inhibited basal and bFGF-stimulated endothelial cell proliferation. This inhibition correlated significantly with reduced cyclin D1 and increased **p21** protein expression. Furthermore, indomethacin reduced pRb phosphorylation. These findings suggest that indomethacin arrests endothelial cell proliferation essential for angiogenesis by modulating cell cycle protein levels. Copyright 2000 Academic Press.

20/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10973403 20539659 PMID: 11089927

Postnatal differentiation of Merkel cells in the **rat** palatine mucosa, with special reference to the timing of peripheral nerve development and the potency of cell mitosis.

Tachibana T; Fujiwara N; Nawa T

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Anatomy and embryology (GERMANY) Nov **2000**, 202 (5) p359-67, ISSN 0340-2061 Journal Code: 4PK
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

The origin and mechanism of the differentiation and proliferation of Merkel cells are enigmatic. A preliminary study in our laboratory showed that Merkel cells in the **rat** palatine mucosa emerge after birth. This is in contrast to the case of similar cells in the skin that differentiate during the embryonic period prior to the establishment of peripheral nerve innervation. We studied immunohistochemically the developmental timings of Merkel cells and peripheral nerves in the **rat** palatine mucosa using antibodies to cytokeratins 18 and 20, PGP 9.5, and CGRP using developing palates of prenatal and postnatal rats. We also studied the potency of mitosis in Merkel cells by immunohistochemistry using antibodies for a cell proliferation marker Ki67 and cyclin D-kinase inhibitors p16, **p21** and **p27**. It was shown that Merkel cells in the **rat** palatine mucosa differentiate postnatally, after the development of peripheral nerve fiber terminals was almost established. The emergence and increase in number of Merkel cells progressed in an anterior-to-posterior wave. Newly appearing Merkel cells were usually negative for anti-cytokeratin 20 antibody but gained affinity for the antibody with progress of maturation. All Merkel cells in the palatine mucosa were negative for anti-Ki67 antibody but positive for anti-**p27** antibody. These results indicate that Merkel cells in the **rat** palatine mucosa are not responsible for the development of peripheral nerve fiber terminals and that these cells differentiate in situ from intraepithelial stem cells.

20/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10970922 21063787 PMID: 11123420
Increased expression of cyclin D1, cyclin E and **p21** (Cip1) associated with decreased expression of **p27** (Kip1) in chemically induced **rat** mammary carcinogenesis.
Jang TJ; Kang MS; Kim H; Kim DH; Lee JI; Kim JR
Department of Pathology, Dongguk University College of Medicine, Sukjang-dong, Kyongju, Kyongbuk 780-714, Korea. taejung@mail.dongguk.ac.kr
Japanese journal of cancer research (Japan) Dec **2000**, 91 (12) p1222-32, ISSN 0910-5050 Journal Code: HBA
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
We induced **rat** mammary tumors in 7-week-old female Sprague-Dawley rats by intragastric administration of 7,12-dimethylbenz(a)anthracene (DMBA), and analyzed by immunohistochemistry the expression of cyclin D1, cyclin E, **p21**(Cip1), and **p27** (Kip1) in carcinomas, atypical tumors, and benign tumors as well as normal mammary glands from the control group. Proliferation status was assessed by immunohistochemistry using bromodeoxyuridine (BrdU). A sequential increase in cyclin D1-, cyclin E-, and **p21** (Cip1)-positive epithelial cells was observed from normal mammary glands, to atypical tumors, to carcinomas. In contrast, carcinomas showed a significantly lower number of epithelial cells immunoreactive to **p27** (Kip1) when compared with atypical tumors, benign tumors and normal mammary glands. The immunoreactivities of BrdU, cyclin D1, cyclin E, and **p21**(Cip1) were positively correlated, whereas that of **p27** (Kip1) appeared inversely correlated to those of the others. Reverse transcriptase-polymerase chain reaction (RT-PCR) and western blot analysis were also performed to determine the mRNA and protein levels of cyclins and cyclin-dependent kinase inhibitors in tumors and normal mammary glands. The protein levels for cyclin D1, cyclin E and **p21**(Cip1) in carcinomas and atypical tumors were significantly higher than those in benign tumors, while normal mammary glands showed negligible expression. On RT-PCR, tumors showed higher mRNA levels of cyclin D1 and cyclin E than those of normal mammary glands. Our results suggest that **rat** mammary carcinogenesis involves increased expression of cyclin D1, cyclin E, and **p21**(Cip1), associated with decreased expression of **p27**(Kip1).

20/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10964459 20576990 PMID: 11134704
Use of osmotic minipumps for sustained drug delivery in **rat** pups: effects on physical and neurobehavioural development.
Doucette TA; Ryan CL; Tasker RA
Department of Anatomy and Physiology, Atlantic Veterinary College, University of Prince Edward Island, C1A 4P3, Charlottetown, PEI, Canada.
Physiology & behavior (UNITED STATES) Oct 1-15 **2000**, 71 (1-2) p207-12, ISSN 0031-9384 Journal Code: P72
Languages: ENGLISH
Document type: Evaluation Studies; Journal Article
Record type: Completed
Osmotic minipumps are often used as an alternative to repetitive injections for prolonged drug delivery in adult rats. The appropriateness of using this technology for sustained drug delivery in newborn rats, however, has not been validated. Our objective was to determine if implantation of osmotic minipumps, and the associated surgical stress, during a critical developmental period, affects early development and subsequent behaviour. SD **rat** pups were assigned to control, minipump, or sham surgery treatment conditions (n=12/group). On P8, pups were briefly anaesthetised with isoflurane in oxygen, and Alzet 1007D osmotic minipumps, loaded with normal saline, were aseptically implanted (removed on P17).

Sham-treated rats received identical treatment (with the exception of pump placement), while control pups were left undisturbed. Development was examined daily using a standard test battery (P9-**P21**), and learning and memory in pups was assessed in a T-maze (P15, P17 and P19). Weight (**P27** and P72), open-field (P25, P26 and **P27**) and novel water maze performance (P60-P72) were examined in the resulting adult. With the exception of a transient decrease in weight gain, pump-treated animals did not differ from either sham or control rats, on any pre- or postweaning assessment. Based on these results we conclude that the use of osmotic minipumps in **rat** pups is a viable alternative to repeated injections for sustained drug delivery.

20/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10902466 20547704 PMID: 11094075

Rat protein tyrosine phosphatase eta suppresses the neoplastic phenotype of retrovirally transformed thyroid cells through the stabilization of **p27**(Kip1).

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Molecular and cellular biology (UNITED STATES) Dec **2000**, 20 (24) p9236-46, ISSN 0270-7306 Journal Code: NGY

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The r-PTPeta gene encodes a **rat** receptor-type protein tyrosine phosphatase whose expression is negatively regulated by neoplastic cell transformation. Here we first demonstrate a dramatic reduction in DEP-1/HPTPeta (the human homolog of r-PTPeta) expression in a panel of human thyroid carcinomas. Subsequently, we show that the reexpression of the r-PTPeta gene in highly malignant **rat** thyroid cells transformed by retroviruses carrying the v-mos and v-ras-Ki oncogenes suppresses their malignant phenotype. Cell cycle analysis demonstrated that r-PTPeta caused G(1) growth arrest and increased the cyclin-dependent kinase inhibitor **p27** (Kip1) protein level by reducing the proteasome-dependent degradation rate. We propose that the r-PTPeta tumor suppressor activity is mediated by **p27**(Kip1) protein stabilization, because suppression of **p27**(Kip1) protein synthesis using **p27** -specific antisense oligonucleotides blocked the growth-inhibitory effect induced by r-PTPeta. Furthermore, we provide evidence that in v-mos- or v-ras-Ki-transformed thyroid cells, the **p27** (Kip1) protein level was regulated by the mitogen-activated protein (MAP) kinase pathway and that r-PTPeta regulated **p27** (Kip1) stability by preventing v-mos- or v-ras-Ki-induced MAP kinase activation.

20/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10857039 20517920 PMID: 10915795

The Rb-CDK4/6 signaling pathway is critical in neural precursor cell cycle regulation.

Ferguson KL; Callaghan SM; O'Hare MJ; Park DS; Slack RS

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Journal of biological chemistry (UNITED STATES) Oct 27 **2000**, 275 (43) p33593-600, ISSN 0021-9258 Journal Code: HIV

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The tumor suppressor, r[redacted]noblastoma (Rb), is involved in both terminal mitosis and neuronal dif[redacted]entiation. We hypothesized tha[redacted]ctivation of the Rb pathway would induce cell cycle arrest in primary neural precursor cells, independent of the proposed function of cyclin-dependent kinases 4/6 (CDK4/6) to sequester the CIP/KIP CDK inhibitors (CKIs) **p21** and **p27** from CDK2. We expressed dominant negative adenovirus mutants of CDKs 2, 4, and 6 (dnCDK2, dnCDK4, and dnCDK6) in neural progenitor cells derived from E12.5 wild type and Rb-deficient **mouse** embryos. In contrast to previous studies, our results demonstrate that in addition to dnCDK2, the dnCDK4/6 mutants can induce growth arrest. Moreover, the dnCDK4/6-mediated inhibition is Rb-dependent. The dnCDK2 partially inhibited cell growth in Rb-deficient cells, suggesting that CDK2 may have additional targets. A previously proposed function of CDK4/6 is CKI sequestration, thereby preventing the resulting inhibition of CDK2, believed to be the key regulator of cell cycle. However, our immunoprecipitations revealed that the dominant negative CDK mutants could arrest cell growth despite their interaction with **p21** and **p27**. Taken together, our results demonstrate that both CDK2 and CDK4/6 are crucial for cell cycle regulation. Furthermore, our data underscore the importance of the Rb regulatory pathway in neuronal development and cell cycle regulation, independent of CKI sequestration.

20/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10780975 20418131 PMID: 10842176
Oncogenic Ras induces p19ARF and growth arrest in **mouse** embryo fibroblasts lacking p21Cip1 and p27Kip1 without activating cyclin D-dependent kinases.
Groth A; Weber JD; Willumsen BM; Sherr CJ; Roussel MF
Department of Tumor Cell Biology and Howard Hughes Medical Institute, St. Jude Children's Research Hospital, Memphis, Tennessee 38105, USA.
Journal of biological chemistry (UNITED STATES) Sep 1 **2000**, 275 (35) p27473-80, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: CA-21765, CA, NCI; CA-56819, CA, NCI; CA-71907, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Oncogenic Ras induces two products of the INK4a/ARF tumor suppressor locus (p16(INK4a) and p19(ARF)) in primary human and rodent fibroblasts, ultimately leading to a permanent state of cell cycle arrest resembling replicative senescence. Whereas p16(INK4a) antagonizes the activities of cyclin D-dependent kinases, p19(ARF) activates the p53 transcription factor. Immortalized rodent fibroblast cell lines that lack INK4a/ARF function, ARF alone, or p53 are resistant to the growth inhibitory effects of oncogenic Ras and instead continue to proliferate and undergo morphological transformation. Primary **mouse** embryo fibroblasts lacking Cip1 and Kip1 genes encoding inhibitors of cyclin-dependent kinase-2 were used to further explore the effects of oncogenic Ras on arrest of the cell division cycle. Although early passage primary fibroblast strains that lack both **p21**(Cip1) and **p27**(Kip1) fail to assemble cyclin D-dependent kinases, oncogenic Ras retained its ability to induce p19(ARF), but not p16(INK4a), protecting Cip/Kip-null cells from proliferating and undergoing transformation. Under these conditions, Ras did not induce G(1) phase arrest but instead triggered DNA synthesis, abnormal nuclear divisions, failure of cytokinesis, and emergence of polyploid cells. Therefore, in the absence of p16(INK4a), **p21**(Cip1), and **p27**(Kip1), oncogenic Ras affects the functions of genes required for completion of the cell cycle.

20/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10757879 99011322 PMID: [redacted]792921
Differentiation and proliferation of primary **rat** hepatocytes cultured as spheroids.
Hamamoto R; Yamada K; Kamihira M; Iijima S
Department of Biotechnology, Graduate School of Engineering, Nagoya University, Chikusa-ku, Nagoya, 464-8603, Japan.
Journal of biochemistry (JAPAN) Nov **1998**, 124 (5) p972-9, ISSN 0021-924X Journal Code: HIF
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
We studied spheroid (multicellular aggregate) formation by hepatocytes and the expression of liver-specific functions such as albumin secretion when hepatocytes were cultured with various extracellular matrices. Hepatocytes cultured on Primaria(R) and poly-D-lysine coated dishes, and in the presence of a polymer, Eudragit, formed spheroids, and they also exhibited higher liver-specific functions and poor growth compared to monolayer cultures. The results indicated that the cell morphological change and cell-cell interaction caused by the spheroid formation were key factors promoting the expression of the liver-specific functions. To elucidate the mechanism underlying the poor growth in spheroids, we examined the HGF signaling pathway. Phosphorylation and down-regulation of the HGF receptor (c-Met proto-oncogene product) were observed for the cells from both monolayer and spheroid cultures, but Ras activation was partly blocked in spheroids. Furthermore, we found that CDK inhibitors, **p21** and **p27**, were highly expressed in spheroids. These results suggested that the reduced Ras signaling and high expression of the CDK inhibitors might cause the lower growth in spheroids. We then examined the relationship between liver-enriched transcription factors (C/EBPalpha and beta) and liver-specific functions. The results revealed that the high expression of C/EBPalpha was maintained during cultures when hepatocytes formed spheroids. Antisense oligonucleotides of C/EBPalpha repressed albumin secretion and the expression of **p21**, suggesting that the transcription factor, C/EBPalpha, may play a crucial role in the growth and differentiation of hepatocytes in spheroids.

20/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10734817 20414685 PMID: 10958672
Uncoupling between phenotypic senescence and cell cycle arrest in aging **p21**-deficient fibroblasts.
Dulic V; Beney GE; Frebourg G; Drullinger LF; Stein GH
Centre de Recherche en Biochimie Macromoleculaire (CRBM)-Centre National de la Recherche Scientifique (CNRS), Montpellier, France. dulic@crbm.cnrs-mop.fr
Molecular and cellular biology (UNITED STATES) Sep **2000**, 20 (18) p6741-54, ISSN 0270-7306 Journal Code: NGY
Contract/Grant No.: AG00947, AG, NIA
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Irreversible G(1) arrest in senescent human fibroblasts is mediated by two inhibitors of cyclin-dependent kinases (Cdks), **p21** (Cip1/SDI1/WAF1) and p16(Ink4A). To determine the physiological and molecular events that specifically require **p21**, we studied senescence in human diploid fibroblasts expressing the human papillomavirus type 16 E6 oncogene, which confers low **p21** levels via enhanced p53 degradation. We show that in late-passage E6 cells, high Cdk activity drives the cell cycle, but population expansion is slowed down by crisis-like events, probably owing to defective cell cycle checkpoints. At the end of lifespan, terminal-passage E6 cells exhibited several aspects of the senescent phenotype and accumulated unphosphorylated pRb and p16. However, both

replication and cyclin-Cdk kinase activity were still not blocked, demonstrating that phenotypic and replicative senescence are uncoupled in the absence of normal **p21** levels. At this stage, E6 cells also failed to upregulate **p27** and inactivate cyclin-Cdk complexes in response to serum deprivation. Eventually, irreversible G(1) arrest occurred coincident with inactivation of cyclin E-Cdk2 owing to association with **p21**. Similarly, when **p21**(-/-) **mouse** embryo fibroblasts reached the end of their lifespan, they had the appearance of senescent cells yet, in contrast to their wild-type counterparts, they were deficient in downregulating bromodeoxyuridine incorporation, cyclin E- and cyclin A-Cdk2 activity, and inhibiting pRb hyperphosphorylation. These data support the model that the critical event ensuring G(1) arrest in senescence is **p21** -dependent Cdk inactivation, while other aspects of senescent phenotype appear to occur independently of **p21**.

20/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10693103 20357372 PMID: 10801895
Peroxisome proliferator-activated receptor gamma ligands inhibit retinoblastoma phosphorylation and G1--> S transition in vascular smooth muscle cells.

Wakino S; Kintscher U; Kim S; Yin F; Hsueh WA; Law RE
Division of Endocrinology, Diabetes, and Hypertension, Department of Medicine, and the Molecular Biology Institute, UCLA, Los Angeles, California 90095, USA.

Journal of biological chemistry (UNITED STATES) Jul 21 **2000**, 275 (29) p22435-41, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: HL58328-03, HL, NHLBI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Peroxisome proliferator-activated receptor gamma (PPARgamma) is a member of the nuclear receptor superfamily that is activated by binding certain fatty acids, eicosanoids, and insulin-sensitizing thiazolidinediones (TZD). The TZD troglitazone (TRO) inhibits vascular smooth muscle cell proliferation and migration both in vitro and in vivo. The precise mechanism of its antiproliferative activity, however, has not been elucidated. We report here that PPARgamma ligands inhibit **rat** aortic vascular smooth muscle cell proliferation by blocking the events critical for G(1) --> S progression. Flow cytometry demonstrated that both TRO and another TZD, rosiglitazone, prevented G(1) --> S progression induced by platelet-derived growth factor and insulin. Movement of cells from G(1) --> S was also inhibited by the non-TZD, natural PPARgamma ligand 15-deoxy-(12,14)Delta prostaglandin J(2) (15d-PGJ(2)), and the mitogen-activated protein kinase pathway inhibitor PD98059. Inhibition of G(1) --> S exit by these compounds was accompanied by a substantial blockade of retinoblastoma protein phosphorylation. TRO and rosiglitazone attenuated both the mitogen-induced degradation of **p27**(kip1) and the mitogenic induction of **p21**(cip1). 15d-PGJ(2) and PD98059 inhibited both the degradation of **p27**(kip1) and the induction of cyclin D1 in response to mitogens. These effects resulted in the inhibition of mitogenic stimulation of cyclin-dependent kinases activated by cyclins D1 and E. These data demonstrate that PPARgamma ligands are antiproliferative drugs that act by modulating cyclin-dependent kinase inhibitors; they may provide a new therapeutic approach for proliferative vascular diseases.

20/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10693041 20357310 PMID: 10791951
Inhibition of the phosphoinositide 3-kinase pathway induces a senescence-like arrest mediated by p27Kip1.

Collado M; Medema RH; Gar[redacted]a-Cao I; Dubuisson ML; Barradas M; Glassford J ; Rivas C; Burgering BM; Se[redacted]ano M; Lam EW

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Journal of biological chemistry (UNITED STATES) Jul 21 **2000**, 275 (29) p21960-8, ISSN 0021-9258 Journal Code: HIV

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

A senescence-like growth arrest is induced in **mouse** primary embryo fibroblasts by inhibitors of phosphoinositide 3-kinase (PI3K). We observed that senescence-like growth arrest is correlated with an increase in **p27** (Kip1) but that down-regulation of other cyclin-dependent kinase (CDK) inhibitors, including p15(INK4b), p16(INK4a), p19(INK4d), and **p21**(Cip1) as well as other negative cell cycle regulators such as p53 and p19(ARF), implies that this senescence-related growth arrest is independent of the activity of p53, p19(ARF), p16(INK4a), and **p21** (Cip1), which are associated with replicative senescence. The **p27** (Kip1) binds to the cyclin/CDK2 complexes and causes a decrease in CDK2 kinase activity. We demonstrated that ectopic expression of **p27**(Kip1) can induce permanent cell cycle arrest and a senescence-like phenotype in wild-type **mouse** embryo fibroblasts. We also obtained results suggesting that the kinase inhibitors LY294002 and Wortmannin arrest cell growth and induce a senescence-like phenotype, at least partially, through inhibition of PI3K and protein kinase B/Akt, activation of the forkhead protein AFX, and up-regulation of **p27**(Kip1)expression. In summary, these observations taken together suggest that **p27** (Kip1) is an important mediator of the permanent cell cycle arrest induced by PI3K inhibitors. Our data suggest that repression of CDK2 activity by **p27** (Kip1) is required for the PI3K-induced senescence, yet **mouse** embryo fibroblasts derived from **p27**(Kip1-/-) mice entered cell cycle arrest after treatment with LY294002. We show that this is due to a compensatory mechanism by which p130 functionally substitutes for the loss of **p27** (Kip1). This is the first description that p130 may have a role in inhibiting CDK activity during senescence.

20/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10686478 20299144 PMID: 10837916

Expression and role of **p27**(kip1) in neuronal differentiation of embryonal carcinoma cells.

Sasaki K; Tamura S; Tachibana H; Sugita M; Gao Y; Furuyama J; Kakishita E ; Sakai T; Tamaoki T; Hashimoto-Tamaoki T

Fifth Department of Internal Medicine, Hyogo College of Medicine, 1-1, Mukogawa-cho, 663-8501, Nishinomiya, Japan.

Brain research. Molecular brain research (NETHERLANDS) May 5 **2000**, 77 (2) p209-21, ISSN 0169-328X Journal Code: MBR

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

We examined the expression and the regulation of **p21**(waf1) and **p27**(kip1) cdk inhibitors in P19 **mouse** embryonal carcinoma (EC) cells following treatment with all-trans retinoic acid (ATRA) to induce neuronal differentiation. The levels of **p27** mRNA and protein increased within 24 h of treatment with ATRA, reaching a plateau 4-5 days later prior to neurite formation. In contrast, levels of **p21** expression remained low until after neurites were extensively formed. Induction of muscle differentiation from P19 cells by treatment with dimethyl sulfoxide caused only transient increases in **p27** levels. In a mutant P19 cell line, RAC65, treatment with ATRA induced neither **p27** accumulation nor neuronal differentiation, but **p21** mRNA expression increased markedly. In contrast, treatment of RAC65 cells with

9-cis retinoic acid induced both **p27** expression and neuronal differentiation. Correlation between **p27** expression and neuronal differentiation was also observed in NT2/D1 human EC cells. Luciferase reporter assays showed that **p27** promoter activity increased in ATRA-treated cells, consistent with the elevation of **p27** mRNA levels. Arrest of neuronal differentiation of P19 cells by okadaic acid resulted in inhibition of **p27** expression, whereas **p21** mRNA expression was greatly enhanced. Conversely, inhibition of **p27** expression by antisense **p27** oligonucleotides resulted in blockade of neuronal differentiation. Taken together, these results strongly suggest that the expression of **p27** is indispensable for neuronal differentiation of EC cells.

20/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10610015 20247106 PMID: 10783329
Suprabasal expression of the human papillomavirus type 16 oncoproteins in **mouse** epidermis alters expression of cell cycle regulatory proteins.
Crish JF; Bone F; Balasubramanian S; Zaim TM; Wagner T; Yun J; Rorke EA; Eckert RL
Department of Physiology and Biophysics, Case Western Reserve University School of Medicine, Cleveland, OH 44106-4970, USA.
Carcinogenesis (ENGLAND) May **2000**, 21 (5) p1031-7, ISSN 0143-3334 Journal Code: C9T
Contract/Grant No.: AR39750, AR, NIAMS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Human papillomavirus (HPV) survives by reactivating DNA replication in post-mitotic cells. In the present study, we describe a **mouse** model of HPV-dependent disease. In these mice, DNA synthesis is activated in suprabasal keratinocytes, leading to acanthosis, parakeratosis and enhanced desquamation. The full-length E6/E7 transcript and two alternately spliced products are produced and in most lines the predominant product is E6*. In the present study, we examine the effects of E6/E7 on cell cycle regulatory protein expression. E6/E7 expression in **mouse** epidermis is correlated with increased levels of the p53, **p21**, **p27**, cdk2, cdk4, cdk6, cyclin D1 and cyclin E regulatory proteins. Hyperproliferation is also observed in the buccal mucosa and the tongue epithelia of E6/E7 mice, and p53 levels are markedly increased in these epithelia. These results suggest that the major changes in cell cycle regulatory protein expression are in response to the presence of E7 and that E6 has a lesser impact.

20/3,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10605038 20281837 PMID: 10820194
Unusual regulation of cyclin D1 and cyclin-dependent kinases cdk2 and cdk4 during in vivo mitotic stimulation of olfactory neuron progenitors in adult **mouse**.
Kastner A; Moyse E; Bauer S; Jourdan F; Brun G
Laboratoire de Biologie Moleculaire et Cellulaire, UMR 49 CNRS, Ecole Normale Superieure de Lyon, France.
Journal of neurochemistry (UNITED STATES) Jun **2000**, 74 (6) p2343-9, ISSN 0022-3042 Journal Code: JAV
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The molecular mechanisms underlying cell cycle control in neuronal progenitors have been investigated with adult **mouse** olfactory epithelium as a model system. Odor receptive neurons of mammalian olfactory epithelium are short-lived and renewed in the adult by mitotic division of

intrinsic neuronal progenitors. Ablation of the synaptic target, olfactory bulb, induces sequentially extensive apoptosis of sensory neurons and then stimulation of progenitor proliferation, peaking at 36 h and 4 days, respectively, postlesion. Known molecular effectors of G1 phase entry have been assessed on protein extracts of olfactory organs sampled at various postbulbectomy times in adult mice. The decay of betaIII-tubulin and olfactory marker protein levels and the rise of proliferating cell nuclear antigen (PCNA) levels, starting 1 and 3 days, respectively, postlesion, provided the kinetic frame of neuronal dynamics. Cyclin D1, cyclin E, and cyclin-dependent kinase cdk2 levels, low in olfactory organ of intact mice, increased 3 days after bulbectomy in parallel with PCNA levels; cdk4 content was initially high and unaffected by lesioning. Western blots of the known cdk inhibitors revealed proliferation-related decreases of p18, **p21**, and **p27** from high expression in intact organs. Immunoprecipitation of cdk2 and cdk4 fractions of protein extracts at 4 days postlesion (mitotic reaction peak) versus control, followed by cyclin D1 immunoblotting, and vice versa, revealed that levels of both cyclin D1/cdk2 and cyclin D1/cdk4 complexes, as well as their kinase activities, were dramatically increased after lesion. In vivo proliferation of olfactory neuronal lineage cells thus involves functional binding of cyclin D1 with cdk2 and cdk4, with differential activation mechanisms for cdk2 and cdk4. In addition, the RT-PCR-detected cyclin D1 mRNA level remained unaffected after bulbectomy, which indicated that the cyclin D1 rise should involve posttranscriptional mechanisms in this in vivo neuronal system. These observations are discussed, along with their relevance to cell cycle control and to olfactory neuron dynamics.

20/3,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10543122 20197667 PMID: 10735620

Control of cyclins, cyclin-dependent kinase inhibitors, **p21** and **p27**, and cell cycle progression in **rat** hepatocytes by extracellular matrix.

Nagaki M; Sugiyama A; Naiki T; Ohsawa Y; Moriwaki H

First Department of Internal Medicine, Gifu University School of Medicine, Japan.

Journal of hepatology (DENMARK) Mar **2000**, 32 (3) p488-96,
ISSN 0168-8278 Journal Code: IBS

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

BACKGROUND/AIMS: The extracellular matrix plays an essential role in the regulation of cell proliferation in different cell types. However, the regulation of cell cycle control in hepatocytes in response to growth factors and extracellular matrix signals is not well understood. The aims of this study were to investigate the expression of key cell cycle control elements, including cyclins, A and D1, and cyclin-dependent kinase inhibitors, **p21** and **p27**, in **rat** hepatocytes in primary culture on dried collagen or Engelbreth-Holm-Swarm in the presence of epidermal growth factor. METHODS: Hepatocytes prepared from Wistar rats were cultured on various extracellular matrix in Williams medium E in the presence or absence of 20 ng/ ml epidermal growth factor. DNA synthesis was measured by [3H]thymidine uptake and mRNA expression of cell cycle-related genes was determined by reverse transcription polymerase chain reaction. RESULTS: Cyclins D1 and A mRNA levels were high at the G1/S boundary in epidermal growth factor-stimulated hepatocytes cultured on dried collagen. In contrast to spread cells, hepatocytes cultured on an Engelbreth-Holm-Swarm gel that were prevented from spreading failed to progress through the G1 phase and enter the S phase. This shape-dependent blockage of cell cycle progression correlated with the up-regulation of the cell cycle inhibitors **p21** and **p27**. CONCLUSIONS: Changes in hepatocyte-extracellular matrix interactions may control hepatocyte growth within the local microenvironment by modulating cell shape and regulating

cyclins and the cyclin-dependent kinase inhibitors **p21** and **p27**.

20/3,AB/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10533001 20175921 PMID: 10710342
Physiological cyclic stretch causes cell cycle arrest in cultured vascular smooth muscle cells.
Chapman GB; Durante W; Hellums JD; Schafer AI
Department of Bioengineering, Rice University, Houston, TX 77005, USA.
American journal of physiology (UNITED STATES) Mar **2000**, 278 (3) pH748-54, ISSN 0363-6135 Journal Code: DKM
Contract/Grant No.: HL-18584, HL, NHLBI; HL-36045, HL, NHLBI; HL-59976, HL, NHLBI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Smooth muscle cells (SMC) are the major cellular component of the blood vessel wall and are continuously exposed to cyclic stretch due to pulsatile blood flow. This study examined the effects of a physiologically relevant level of cyclic stretch on **rat** aortic vascular SMC proliferation. Treatment of static SMC with serum, platelet-derived growth factor, or thrombin stimulated SMC proliferation, whereas exposure of SMC to cyclic stretch blocked the proliferative effect of these growth factors. The stretch-mediated inhibition in SMC growth was not due to cell detachment or increased cell death. Flow cytometry analysis revealed that cyclic stretch increased the fraction of SMC in the G(0)/G(1) phase of the cell cycle. Stretch-inhibited G(1)/S phase transition was associated with a decrease in retinoblastoma protein phosphorylation and with a selective increase in the cyclin-dependent kinase inhibitor **p21**, but not **p27**. These results demonstrate that cyclic stretch inhibits SMC growth by blocking cell cycle progression and suggest that physiological levels of cyclic stretch contribute to vascular homeostasis by inhibiting the proliferative pathway of SMC.

20/3,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10515241 20117476 PMID: 10650125
Immunohistochemical examination of the INK4 and Cip inhibitors in the **rat** neonatal cerebellum: cellular localization and the impact of protein calorie malnutrition.
Shambaugh GE; Haines GK; Koch A; Lee EJ; Zhou Jn; Pestell R
Department of Medicine, Northwestern University Medical School and Veterans Affairs Chicago Health Care System, Lakeside Division, 333 East Huron St., Chicago, IL 60611-3008, USA.
Brain research (NETHERLANDS) Feb 7 **2000**, 855 (1) p11-22, ISSN 0006-8993 Journal Code: B5L
Contract/Grant No.: AI40987, AI, NIAID; R29CA70897, CA, NCI; RO1CA75503, CA, NCI; +
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Expression of the cyclin-dependent kinase inhibitors (CKIs) has been linked to the inhibition of cellular proliferation and the induction of differentiation. Based on structure function analysis, two distinct families of CDKIs, the INK4 and the Cip/Kip family have been identified. The INK4 family member p16(Ink4), and the Cip/Kip protein **p27**(Kip1) have been implicated in normal development of the CNS and cerebellum. Recent studies have suggested a functional inter-dependence between the CKI and the abundance of cyclin D1 in orchestrating growth factor-induced cellular proliferation. The neonatal **rat** cerebellum undergoes proliferative growth and differentiation, localized to distinct

topographical regions and cell types. The cell type and the temporal profile of CKI expression during postnatal cerebellar development had not been described. The current studies determined the specific cerebellar cell types in which the CKIs were expressed during post natal development by co-staining for cell-type specific markers. p16(Ink4a) and **p27**(Kip1) immunostaining was identified in both neurons and glial cells, increasing progressively between postnatal days 6 to 13 into adulthood. By contrast, neuronal and glial cell **p21**(Cip1) staining was prominent at days 6-11 and decreased thereafter. Cyclin D1 was expressed in the proliferating external granular cells, with occassional staining in the molecular, and internal granular layers. Dual immunostaining demonstrated cyclin D1 within cells expressing CKI (p16(Ink4a), **p21**(Cip1),**p27** (Kip1)). Cerebellar cellular growth arrest, induced by protein-calorie malnutrition, inhibited cyclin D1 protein levels without affecting CKI immunostaining suggesting CKI do not mediate the developmental arrest. These results demonstrate that the CKIs are induced by differentiation cues in specific cell types with distinct kinetics in the developing cerebellum in vivo.

20/3,AB/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10509982 20127944 PMID: 10660624
The caudal-related homeodomain protein Cdx1 inhibits proliferation of intestinal epithelial cells by down-regulation of D-type cyclins.
Lynch J; Suh ER; Silberg DG; Rulyak S; Blanchard N; Traber PG
Division of Gastroenterology, Department of Medicine and Genetics, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA.
Journal of biological chemistry (UNITED STATES) Feb 11 **2000**, 275 (6) p4499-506, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: P30-DK50306, DK, NIDDK; PO1-DK49210, DK, NIDDK; T32-DK07066, DK, NIDDK
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Cdx1 is a homeodomain transcription factor that regulates intestine-specific gene expression. Experimental evidence suggests that Cdx1 may be involved in cell cycle regulation, but its role is ill defined and the mechanisms have not been explored. We used stable transfection of inducible constructs and transient expression with a replication-deficient adenovirus to induce Cdx1 expression in **rat** IEC6 cells, a non-transformed intestinal epithelial cell line that does not express Cdx1 protein. Expression of Cdx1 markedly reduced proliferation of IEC6 cells with accumulation of cells in the G(0)/G(1) phase of the cell cycle. Cell cycle arrest was accompanied by an increase in the hypophosphorylated forms of the retinoblastoma protein (pRb) and the pRb-related p130 protein. Protein levels of multiple cyclin-dependent kinase inhibitors were either unchanged (p16, p18, **p21**, **p27**, and p57) or were not detected (p15 and p19). Most significantly, levels of cyclins D1 and D2 were markedly diminished with Cdx1 expression, but not cyclins D3, E, or the G(1) kinases. Additionally, cyclin-dependent kinase-4 activity was decreased in association with decreased cyclin D protein. We conclude that Cdx1 regulates intestinal epithelial cell proliferation by inhibiting progression through G(0)/G(1), most likely via modulation of cyclin D1 and D2 protein levels.

20/3,AB/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10487550 20125636 PMID: 10657906
Overexpression of **p21** protein in radiation-transformed **mouse** 10T(1/2) cell clones.
Krolewski B; Little JB
Harvard School of Public Health, Department of Cancer Cell Biology,

Boston, Massachusetts 0211[redacted] USA.
Molecular carcinogenes[redacted] (UNITED STATES) Feb **2000**, [redacted]7 (2)
p141-8, ISSN 0899-1987 Journal Code: AEQ
Contract/Grant No.: CA-47542, CA, NCI; ES-00002, ES, NIEHS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

In order to investigate the hypothesis that aberrant expression of cell-cycle regulatory proteins may represent early events in the process of carcinogenesis, levels of expression of the negative regulators **p21** (waf1/cip1) (**p21**), **p27**(kip1) (**p27**), and p16(ink4a) (p16) and/or the positive regulators cyclin D(1) and cyclin E were examined by western blot analysis in cells transformed in vitro by ionizing radiation. The levels of these proteins in 12 independently derived **mouse** 10T(1/2) cell clones transformed by 1.5 Gy of alpha radiation were compared with those in nine similarly derived nontransformed control clones. Constitutive levels of **p21** were very low in all control clones, whereas **p21** expression was significantly elevated in nine of 12 transformed clones. Two of the three transformed clones displaying low levels of **p21** expressed increased levels of p53. **p21** regulation was also altered in response to radiation in transformed clones as compared with controls, only minimal induction was observed 4 h following gamma irradiation. Western blot analysis indicated a constant expression of **p27** protein but slightly decreased levels of p16 in these transformed clones. Cyclin D(1) was overexpressed in 11 of 12 transformed clones; in only two of these were the levels of cyclin E elevated. Overall, the results suggest that alterations in the expression of cell cycle regulatory proteins may represent important events in radiation-induced oncogenic transformation in vitro. Although the specific alterations vary among different transformed clones, overexpression and aberrant regulation of **p21** appear to be the most frequent ones. Copyright 2000 Wiley-Liss, Inc.

20/3,AB/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10471439 20090553 PMID: 10623657
Early increase in cyclin-D1 expression and accelerated entry of **mouse** hepatocytes into S phase after administration of the mitogen 1, 4-Bis[2-(3,5-Dichloropyridyloxy)] benzene.
Ledda-Columbano GM; Pibiri M; Loi R; Perra A; Shinozuka H; Columbano A
Department of Toxicology, Oncology and Molecular Pathology Unit, University of Cagliari, Cagliari, Italy. columbano@vaxcal.unica.it
American journal of pathology (UNITED STATES) Jan **2000**, 156 (1) p91-7, ISSN 0002-9440 Journal Code: 3RS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

We have previously demonstrated that hepatocyte proliferation induced by the mitogen 1,4-bis[2-(3,5-dichloropyridyloxy)] benzene (TCPOBOP) is independent of changes in cytokines, immediate early genes, and transcription factors that are considered to be necessary for regeneration of the liver after partial hepatectomy (PH) or necrosis. To further investigate the differences between mitogen-induced **mouse** hepatocyte proliferation and liver regeneration after PH, we have measured the expression of cyclin D1, cyclin D3, cyclin E, and cyclin A and of the cyclin-dependent kinases CDK2, CDK4, and CDK6. The involvement of the cyclin-dependent kinase inhibitors **p21** and **p27** and of the oncosuppressor gene p53 was also examined at different times after stimulation of hepatocyte proliferation. Results showed that a single administration of TCPOBOP caused a very rapid increase in the levels of cyclin D1, a G1 protein, when compared with two thirds PH (8 hours versus 30 hours). The early increase in cyclin D1 protein levels was associated with a faster onset of increased expression of S-phase-associated cyclin A

(24 hours versus 36 hours with PH mice). Accordingly, measurement of bromodeoxyuridine (BrdU) incorporation revealed [redacted], although approximately 8% of hepatocytes were BrdU-positive as early as 24 hours after TCPOBOP, no significant changes in BrdU incorporation were observed at the same time point after two thirds PH. The expression of other proteins involved in cell cycle control, such as cyclin-dependent kinases (CDK4, CDK2, CDK6), was also analyzed. Results showed that expression of CDK2 was induced much more rapidly in TCPOBOP-treated mice (2 hours) than in mice subjected to PH (36 hours). A different pattern of expression in the two models of hepatocyte proliferation, although less dramatic, was also observed for CDK4 and CDK6. Expression of the CDK inhibitors **p21** and **p27** and the oncosuppressor gene p53 variably increased after two thirds PH, whereas basically no change in protein levels was found in TCPOBOP-treated mice. The results demonstrate that profound differences in many cell cycle-regulatory proteins exist between direct hyperplasia and compensatory regeneration. Cyclin D1 induction is one of the earlier events in hepatocyte proliferation induced by the primary mitogen TCPOBOP and suggests that a direct effect of the mitogen on this cyclin may be responsible for the rapid onset of DNA synthesis observed in TCPOBOP-induced hyperplasia.

20/3,AB/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10455814 20080778 PMID: 10612647
Aging impairs induction of cyclin-dependent kinases and down-regulation of **p27** in **mouse** CD4(+) cells.
Tamir A; Miller RA
Department of Pathology, University of Michigan School of Medicine, Ann Arbor, Michigan 48109, USA.
Cellular immunology (UNITED STATES) Nov 25 **1999**, 198 (1) p11-20, ISSN 0008-8749 Journal Code: CQ9
Contract/Grant No.: AG08808, AG, NIA; AG09801, AG, NIA
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
To define the link between the early activation defects and the impaired proliferation response of cells from old mice, we characterized the influence of age on expression and activity of proteins that participate in cell-cycle regulation. We found that aging led to significant declines in the ability of **mouse** CD4(+) T cells to respond to CD3 and CD28 stimuli by induction of the cyclin-dependent kinases CDK2, CDK4, and CDK6, whether the defect was assessed by protein level or functional activity. Induction of CDK2 activity was also impaired in cells from old mice that were activated with PMA plus ionomycin, stimuli that bypass the TCR/CD3 complex, or by CD3/CD28 in the presence of IL-2, indicating that the age-related changes lie, at least in part, downstream of the enzymes activated by these stimuli. We also noted an impairment in the ability of CD4(+) cells from old mice to down-regulate the CDK inhibitor **p27** after activation, but we found no change in induction of **p21**, an inhibitor of CDK that may also play other roles in cell-cycle control. Altered CDK activation is likely to mediate the age-related decline in T cell proliferation to polyclonal stimulation. Copyright 1999 Academic Press.

20/3,AB/22 (Item 22 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10454276 20074214 PMID: 10601001
Cyclin E-**p27** opposition and regulation of the G1 phase of the cell cycle in the murine neocortical PVE: a quantitative analysis of mRNA in situ hybridization.
Delalle I; Takahashi T; Nowakowski RS; Tsai LH; Caviness VS

Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston 02114, USA. [redacted]ellale@partners.org
Cerebral cortex (UNITED STATES) Dec **1999**, 9 (8) p824-32,
ISSN 1047-3211 Journal Code: BI9
Contract/Grant No.: NS12005, NS, NINDS; NS33433, NS, NINDS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
We have analyzed the expression patterns of mRNAs of five cell cycle related proteins in the ventricular zone of the neocortical cerebral wall over the course of the neuronogenetic interval in the **mouse**. One set of mRNAs (cyclin E and **p21**) are initially expressed at high levels but expression then falls to a low asymptote. A second set (**p27**, cyclin B and cdk2) are initially expressed at low levels but ascend to peak levels only to decline again. These patterns divide the overall neuronogenetic interval into three phases. In phase 1 cyclin E and **p21** levels of mRNA expression are high, while those of mRNAs of **p27** , cdk2 and cyclin B are low. In this phase the fraction of cells leaving the cycle after each mitosis, Q, is low and the duration of the G1 phase, TG1, is short. In phase 2 levels of expression of cyclin E and **p21** fall to asymptote while levels of expression of mRNA of the other three proteins reach their peaks. Q increases to approach 0.5 and TG1 increases even more rapidly to approach its maximum length. In phase 3 levels of expression of cyclin E and **p21** mRNAs remain low and those of the mRNAs of the other three proteins fall. TG1 becomes maximum and Q rapidly increases to 1.0. The character of these phases can be understood in part as consequences of the reciprocal regulatory influence of **p27** and cyclin E and of the rate limiting functions of **p27** at the restriction point and of cyclin E at the G1 to S transition.

20/3,AB/23 (Item 23 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10453205 20107553 PMID: 10642941
Changes in expression of cell cycle regulators and their hepatic lobular distribution in partial hepatectomy-induced regenerating **rat** liver.
Jeong JS; Lee JH; Kim HI; Park JI
Department of Pathology, Dong-A University College of Medicine, Pusan, Korea. jsjung1@daunet.donga.ac.kr
Journal of Korean medical science (KOREA (SOUTH)) Dec **1999**, 14 (6) p635-42, ISSN 1011-8934 Journal Code: AH4
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Partial hepatectomy (PH) endorses quiescent hepatocytes to reenter the cell cycle. The regenerating liver returns to its preresection weight after 7 days, following one or two cell division and maintains nearly its original volume after then. We focused on the inhibition of further hepatocyte proliferation, hypothesizing possible involvement of cell cycle upregulators and inhibitors. We studied protein levels in expression of cyclins, cyclin dependent kinases (CDKs) and CDK inhibitors (CKIs), and their in situ hepatic lobular distributions in partial hepatectomized **rat** liver. Cyclin E was expressed in the same levels in normal liver and after PH. Expression of cyclin A, not detected in normal liver, increased in following times after PH and reached a maximum at 7 day. CDK2 and 4 showed increased expression toward terminal period. Contradictory findings of cyclin A and these CDKs might play an important role in the inhibition of further cell division, although still unclear. Constitutively expressed CDK6 decreased after 1 day. p18 showed peak expression within 1 day, and p16, **p21**, **p27** and p57 were stronger at terminal periods. During the expected period of their activity, intranuclear translocations were observed in cyclin E, p18 and p16. There was no evidence of regional distribution in hepatic lobular architecture, instead, diffuse in situ expression, corroborating synchronous event, was found.

20/3,AB/24 (Item 24 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10415309 20035067 PMID: 10564100
Expression and modulation of p42/p44 MAPKs and cell cycle regulatory proteins in **rat** pancreas regeneration.
Morisset J; Aliaga JC; Calvo EL; Bourassa J; Rivard N
Service de gastro-enterologie, Departement de Medecine, Faculte de Medecine, Universite de Sherbrooke, Sherbrooke, Quebec, Canada J1H 5N4. jmori7@courrier.usherb.ca
American journal of physiology (UNITED STATES) Nov **1999**, 277 (5 Pt 1) pG953-9, ISSN 0002-9513 Journal Code: 3U8
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Pancreatic growth occurs after CCK, CCK-induced pancreatitis, and pancreatectomy; the mechanisms involved remain unknown. This study evaluates mitogen-activated protein kinase (MAPK) activation and expression of cell cycle regulatory proteins after pancreatectomy to understand the cellular and molecular mechanisms involved in pancreas regeneration. Rats were killed 1-12 days after pancreatectomy, and p42/p44 MAPK activation, expression of the cyclins D and E, cyclin-dependent kinase (Cdk)-2 activity, retinoblastoma protein (pRb) hyperphosphorylation, and expression of the cyclin kinase inhibitors p15, **p21**, and **p27** were examined. Pancreatic remnants exhibited sustained p42/p44 MAPK activation within 8 h. Cyclins D1 and E showed maximal expression after 2 and 6 days, coinciding with maximal hyperphosphorylation of pRb and Cdk2 activity. The expression of p15 vanished after 12 h, **p27** disappeared gradually, and **p21** increased early. The **p27** complexed with Cdk2 dissociated after 2 days, whereas **p21** associated in a reverse fashion. In conclusion, sustained activation of p42/p44 MAPKs and Cdk2 along with overexpression of cyclins D1 and E and reduction of p15 and **p27** cyclin inhibitors occurred early after pancreatectomy and are active factors involved in signaling that leads to pancreas regeneration.

20/3,AB/25 (Item 25 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10397629 99438008 PMID: 10508164
Cyclins D1 and D2 mediate myc-induced proliferation via sequestration of **p27**(Kip1) and **p21**(Cip1).
Perez-Roger I; Kim SH; Griffiths B; Sewing A; Land H
Imperial Cancer Research Fund, 44 Lincoln's Inn Fields, London WC2A 3PX, UK.
EMBO journal (ENGLAND) Oct 1 **1999**, 18 (19) p5310-20, ISSN 0261-4189 Journal Code: EMB
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Cyclin E-Cdk2 kinase activation is an essential step in Myc-induced proliferation. It is presumed that this requires sequestration of G(1) cell cycle inhibitors **p27**(Kip1) and **p21** (Cip1) (Ckis) via a Myc-induced protein. We provide biochemical and genetic evidence to show that this sequestration is mediated via induction of cyclin D1 and/or cyclin D2 protein synthesis rates. Consistent with this conclusion, primary cells from cyclin D1(-/-) and cyclin D2(-/-) **mouse** embryos, unlike wild-type controls, do not respond to Myc with increased proliferation, although they undergo accelerated cell death in the absence of serum. Myc sensitivity of cyclin D1(-/-) cells can be restored by retroviruses expressing either cyclins D1, D2 or a cyclin D1 mutant forming kinase-defective, Cki-binding cyclin-cdk complexes. The sequestration function of D cyclins thus appears essential for Myc-induced cell cycle

progression but dispensable for apoptosis.

20/3,AB/26 (Item 26 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10373475 99455018 PMID: 10523650
p57(Kip2) stabilizes the MyoD protein by inhibiting cyclin E-Cdk2 kinase activity in growing myoblasts.
Reynaud EG; Pelpel K; Guillier M; Leibovitch MP; Leibovitch SA
Laboratoire de Genetique Oncologique UMR 1599 CNRS, Institut Gustave Roussy, 94805 Villejuif, France.
Molecular and cellular biology (UNITED STATES) Nov **1999**, 19 (11) p7621-9, ISSN 0270-7306 Journal Code: NGY
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
We show that expression of p57(Kip2), a potent tight-binding inhibitor of several G(1) cyclin-cyclin-dependent kinase (Cdk) complexes, increases markedly during C2C12 myoblast differentiation. We examined the effect of p57(Kip2) on the activity of the transcription factor MyoD. In transient transfection assays, transcriptional transactivation of the **mouse** muscle creatine kinase promoter by MyoD was enhanced by the Cdk inhibitors. In addition, p57(Kip2), **p21**(Cip1), and **p27** (Kip1) but not p16(Ink4a) induced an increased level of MyoD protein, and we show that MyoD, an unstable nuclear protein, was stabilized by p57(Kip2). Forced expression of p57(Kip2) correlated with hypophosphorylation of MyoD in C2C12 myoblasts. A dominant-negative Cdk2 mutant arrested cells at the G(1) phase transition and induced hypophosphorylation of MyoD. Furthermore, phosphorylation of MyoD by purified cyclin E-Cdk2 complexes was inhibited by p57(Kip2). In addition, the NH2 domain of p57(Kip2) necessary for inhibition of cyclin E-Cdk2 activity was sufficient to inhibit MyoD phosphorylation and to stabilize it, leading to its accumulation in proliferative myoblasts. Taken together, our data suggest that repression of cyclin E-Cdk2-mediated phosphorylation of MyoD by p57(Kip2) could play an important role in the accumulation of MyoD at the onset of myoblast differentiation.

20/3,AB/27 (Item 27 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10333962 99223107 PMID: 10208426
Cross-talk between the Smad1 and Ras/MEK signaling pathways for TGFbeta.
Yue J; Frey RS; Mulder KM
Department of Pharmacology, Pennsylvania State University College of Medicine, Hershey 17033, USA.
Oncogene (ENGLAND) Mar 18 **1999**, 18 (11) p2033-7, ISSN 0950-9232 Journal Code: ONC
Contract/Grant No.: CA51425, CA, NCI; CA54816, CA, NCI; CA68444, CA, NCI;
+
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Our previous data demonstrated that Ras activation was necessary and sufficient for transforming growth factor-beta (TGFbeta)-mediated Erk1 activation, and was required for TGFbeta up-regulation of the Cdk inhibitors (CKI's) **p27**(Kip1) and **p21**(Cip1) (KM Mulder and SL Morris, J. Biol. Chem., 267, 5029-5031, 1992; MT Hartsough and KM Mulder, J. Biol. Chem., 270, 7117-7124, 1995; MT Hartsough et al., J. Biol. Chem., 271, 22368-22375, 1996 and J Yue et al., Oncogene, 17, 47-55, 1998). Here we examined the role of Ras in TGFbeta-mediated effects on a **rat** homolog of Smad1 (termed RSmad1). We demonstrate that both TGFbeta and bone morphogenetic protein (BMP) can induce endogenous Smad1 phosphorylation in intestinal epithelial cells (IECs). The combination of transient expression

of RSmad1 and TGFbeta treatment had an additive effect on induction of the TGFbeta-responsive reporter 3TP-lux. Either inactivation of Ras by stable, inducible expression of a dominant-negative mutant of Ras (RasN17) or addition of MAP and ERK kinase (MEK) inhibitor PD98059 to cells significantly decreased the ability of both TGFbeta and BMP to induce phosphorylation of endogenous Smad1 in IECs. Moreover, either inactivation of Ras or addition of PD98059 to IEC 4-1 cells inhibited the ability of RSmad1 to regulate 3TP luciferase activity in both the presence and absence of TGFbeta. Collectively, our data indicate that TGFbeta can regulate RSmad1 function in epithelial cells, and that the Ras/MEK pathway is partially required for TGFbeta-mediated regulation of RSmad1.

20/3,AB/28 (Item 28 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10327153 99111141 PMID: 9815583
Reciprocal changes in **p27**(Kip1) and **p21**(Cip1) in growth inhibition mediated by blockade or overstimulation of epidermal growth factor receptors.
Fan Z; Shang BY; Lu Y; Chou JL; Mendelsohn J
The University of Texas M.D. Anderson Cancer Center, Houston, Texas 77030, USA.
Clinical cancer research (UNITED STATES) Nov **1997**, 3 (11) p1943-8, ISSN 1078-0432 Journal Code: C2H
Contract/Grant No.: CA42060, CA, NCI; CA68425, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Many human epithelial tumors express high levels of epidermal growth factor (EGF) receptors. A human-**mouse** chimeric version of anti-EGF receptor monoclonal antibody (mAb) C225, which blocks receptor activation and produces inhibition of cell proliferation, is currently being investigated in clinical trials. When cells bear high numbers of EGF receptors, either complete blockade of receptors with mAb 225 or full activation of receptors with EGF results in inhibition of proliferation. In the present study, we have explored the molecular mechanisms explaining how a receptor inhibitor, mAb 225, and a receptor activator, EGF, can both produce growth inhibition of A431 human squamous epithelial carcinoma cells. We reported previously that inhibition of A431 cells by EGF is associated with up-regulation of **p21**(Cip1). We now demonstrate that mAb 255-mediated inhibition is associated with up-regulation of **p27** (Kip1), which binds to and inactivates cyclin-dependent kinase-2 activity and produces cell cycle arrest in G1. Furthermore, inhibition by mAb 225 can be overcome by titrating the cultures with increasing concentrations of EGF, which is accompanied by a concurrent fall in the level of **p27** (Kip1). At properly titrated concentrations of mAb 225 and EGF, the inhibitory activities of both mAb 225 and EGF are counterbalanced and abolished. When EGF concentrations reach levels high enough to compete with mAb to produce near-saturating levels of receptor activation, **p27** (Kip1) falls below basal levels; however, the concomitant marked rise in the level of **p21**(Cip1) results in growth inhibition. Our data suggest that although **p27**(Kip1) and **p21** (Cip1) are induced and act independently, they play reciprocal roles in mediating inhibition of A431 cell growth by blockade of EGF receptors with mAb 225 and by activation of receptors with saturating concentrations of EGF.

20/3,AB/29 (Item 29 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10326908 99124386 PMID: 9927196
Coordinated changes in cell cycle machinery occur during keratinocyte terminal differentiation.
Martinez LA; Chen Y; Fischer SM; Conti CJ

The University of Texas M[redacted] Anderson Cancer Center, Science Park Research Division, Smithville, USA.
Oncogene (ENGLAND) Jan 14 **1999**, 18 (2) p397-406, ISSN 0950-9232 Journal Code: ONC
Contract/Grant No.: CA 42157, CA, NCI; CA 57596, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Differentiation of cells is typically marked by a cessation of proliferation with a concurrent entrance into a distinct metabolic state marked by tissue specific gene expression. The mechanism by which the cell exits the cell cycle in this process is poorly understood. To determine the potential roles of the cell cycle machinery in the regulation of the terminal differentiation process of epidermal cells, we selected a well characterized in vitro model in which primary **mouse** keratinocytes are induced to differentiate in response to a raised calcium ion concentration in the medium. The withdrawal from the cell cycle correlates very well with a number of changes in the cell cycle machinery. Changes in the phosphorylation status of the Rb family of proteins occurs coordinately with an increased association of **p21**, **p27** and p57 with cdk2. Furthermore, we find that inhibition of cdk2 activity is not sufficient to elicit changes that occur during keratinocyte differentiation. Finally, the previously described v-Ha-ras block of keratinocyte differentiation correlates with altered regulation of both cyclin D1 and cdk2 suggesting that these genes may play a role in the Ha-ras transformation of a keratinocyte.

20/3,AB/30 (Item 30 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10322583 99018077 PMID: 9799664
Expressions and activities of cell cycle regulatory molecules during the transition from myocyte hyperplasia to hypertrophy.
Poolman RA; Brooks G
Cardiovascular Cellular and Molecular Biology, The Rayne Institute, St Thomas>> Hospital, London, SE1 7EH, UK.
Journal of molecular and cellular cardiology (ENGLAND) Oct **1998**, 30 (10) p2121-35, ISSN 0022-2828 Journal Code: J72
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The role of cell cycle dependent molecules in controlling the switch from cardiac myocyte hyperplasia to hypertrophy remains unclear, although in the **rat** this process occurs between day 3 and 4 after birth. In this study we have determined (1) cell cycle profiles by fluorescence activated cell sorting (FACS); and (2) expressions, co-expressions and activities of a number of cyclins, cyclin-dependent kinases (CDKs) and CDK inhibitors by reverse transcriptase-polymerase chain reaction (RT-PCR), immunoblotting and in vitro kinase assays in freshly isolated **rat** cardiac myocytes obtained from 2, 3, 4 and 5-day-old animals. The percentage of myocytes found in the S phase of the cell cycle decreased significantly during the transition from hyperplasia to hypertrophy (5.5, 3.5, 2.3 and 1.9% of cells in 2-, 3-, 4- and 5-day-old myocytes, respectively, $P<0.05$), concomitant with a significant increase in the percentage of G0/G1 phase cells. At the molecular level, the expressions and activities of G1/S and G2/M phase acting cyclins and CDKs were downregulated significantly during the transition from hyperplasia to hypertrophy, whereas the expressions and activities of G1 phase acting cyclins and CDKs were upregulated significantly during this transition. In addition, **p21**(CIP1)- and **p27** (KIP1)- associated CDK kinase activities remained relatively constant when histone H1 was used as a substrate, whereas phosphorylation of the retinoblastoma protein was upregulated significantly during the transition from hyperplasia to hypertrophy. Thus, there is a progressive and significant G0/G1 phase blockade during the transition from myocyte

hyperplasia to hypertrophy. Whilst CDK2 and cdc2 may be pivotal in the withdrawal of cardiac myocytes from the cell cycle, CDK4 and CDK6 may be critical for maintaining hypertrophic growth of the myocyte during development. Copyright 1998 Academic Press

20/3,AB/31 (Item 31 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10308602 98334606 PMID: 9668055
Rac and Cdc42 are potent stimulators of E2F-dependent transcription capable of promoting retinoblastoma susceptibility gene product hyperphosphorylation.
Gjoerup O; Lukas J; Bartek J; Willumsen BM
Department of Molecular and Cellular Biology, University of Copenhagen, Oster Farimagsgade 2A, DK 1353, Copenhagen K, Denmark.
Journal of biological chemistry (UNITED STATES) Jul 24 **1998**, 273 (30) p18812-8, ISSN 0021-9258 Journal Code: HIV
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The Rho family of GTPases plays an important and diverse role in reorganization of the actin cytoskeleton, transcriptional regulation, and multiple aspects of cell growth. Our study has examined their potential links to the cell cycle machinery. We find that constitutively active mutants of Rac and Cdc42, but not Rho, are potent inducers of E2F transcriptional activity in NIH 3T3 fibroblasts. Furthermore, activated Rac and Cdc42, but again not Rho, are capable of inducing cyclin D1 accumulation and pRB hyperphosphorylation in serum-deprived cells, outlining one route leading to enhanced E2F-mediated transcription. The inhibitory effect of the cyclin-dependent kinase inhibitors, p16(ink4), **p21**(cip1), and **p27**(cip) on Rac/Cdc42-mediated E2F transcription corroborates a role for pRB family members and their functional inactivation by cyclin-dependent kinases in generating E2F activity. While the up-regulation of E2F transcriptional activity by Rac or Cdc42, not Rho, suffices for entry into S phase and DNA synthesis in **Rat**-1 R12 cells, this is clearly not the case in NIH 3T3, where additional requirements must exist.

20/3,AB/32 (Item 32 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10305199 98237509 PMID: 9578398
Cell cycle-related gene expression in the adult **rat** brain: selective induction of cyclin G1 and p21WAF1/CIP1 in neurons following focal cerebral ischemia.
van Lookeren Campagne M; Gill R
Hoffmann-La Roche Ltd, PRPN, Basel, Switzerland.
Neuroscience (UNITED STATES) Jun **1998**, 84 (4) p1097-112, ISSN 0306-4522 Journal Code: NZR
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The present studies were initiated to investigate whether p53 transactivated target genes are induced in a **rat** model of focal cerebral ischemia. Therefore, we applied in situ hybridization, immunocytochemistry and western blotting to study the temporal and spatial expression of p53 and its transcriptional targets Bax, **p21** and cyclin G1 following permanent middle cerebral artery occlusion in the **rat**. Cyclin G1 immunoreactivity was constitutively expressed in the nuclei of cells in the choroid plexus and ependymal cell layer and in the cytoplasm of cell bodies and dendrites of pyramidal neurons of the cerebral cortex. Cyclin G1 messenger RNA and protein levels transiently increased to 150% of contralateral levels in neurons of the ipsilateral frontal and parietal

cortex and striatum 3 h following middle cerebral artery occlusion. A low level of constitutively expressed **p21** messenger RNA and protein was found in nuclei of cells in the choroid plexus, oligodendrocytes and neurons. **p21** messenger RNA and protein levels gradually increased to 250% and 140% of contralateral levels in areas bordering the infarct core up to 6 h following middle cerebral artery occlusion. In contrast, p53 and Bax messenger RNA and protein levels, and protein levels of **p27**, cyclin-dependent kinase 5, p35 and cyclin E decreased in the infarct core and border areas with time after middle cerebral artery occlusion. The selective up-regulation of cyclin G1 and **p21** in neurons in the border zone of a focal ischemic infarct indicates their involvement in an adaptive response to ischemic injury. The possible participation of cyclin G1 and **p21** in a signal transduction pathway associated with ischemia-induced cellular stress is discussed.

20/3,AB/33 (Item 33 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10299091 98173027 PMID: 9514094
Molecular analysis of two mammary carcinoma cell lines at the transcriptional level as a model system for progression of breast cancer.
Schiemann S; Schwirzke M; Brunner N; Weidle UH
Boehringer Mannheim GmbH, Penzberg, Germany.
Clinical & experimental metastasis (ENGLAND) Feb **1998**, 16 (2) p129-39, ISSN 0262-0898 Journal Code: DFC
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
As a model system for the identification of genes involved in the progression of human breast cancer, differential gene expression in cell lines MCF-7 and MCF-7ADR was investigated. The latter cell line is derived from the former. Cell line MCF-7 is estrogen receptor-positive, vimentin-negative and uninvasive in the Matrigel outgrowth assay and in the nude **mouse** , while MCF-7ADR is estrogen receptor-negative, hormone-resistant, vimentin-positive, invasive in the Matrigel outgrowth assay and in the nude **mouse** and resistant to adriamycin due to overexpression of glycoprotein gp170. We have shown that tumor progression in this model system is mediated by transcriptional regulation of mitochondria-related genes, proteases, transmembrane receptors and cell cycle-related gene proteins. Among the genes differentially regulated at the transcriptional level in the cell lines MCF-7 and MCF-7ADR are a new mitochondrial transcript, mitochondrial creatine kinase, matrix metalloproteinase-1, stromelysin-3, urokinase and its receptor, tissue factor, E-cadherin, epidermal growth factor receptor, transmembrane proteins Mat-8 and progression associated protein (PAP), cyclin E, cyclin-dependent kinase-2 and cell cycle inhibitory proteins p16, **p21** and **p27**.

20/3,AB/34 (Item 34 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10262427 99400573 PMID: 10469613
Reduced expression of the CDK inhibitor **p27**(KIP1) in **rat** two-stage bladder carcinogenesis and its association with expression profiles of **p21**(WAF1/Cip1) and p53.
Lee CC; Ichihara T; Yamamoto S; Wanibuchi H; Sugimura K; Wada S; Kishimoto T; Fukushima S
First Department of Pathology and Department of Urology, Osaka City University Medical School, 1-4-3 Asahi-machi, Abeno-ku, Osaka 545-8585, Japan. ccrichlee@aol.com
Carcinogenesis (ENGLAND) Sep **1999**, 20 (9) p1697-708, ISSN 0143-3334 Journal Code: C9T
Languages: ENGLISH

Document type: Journal Article
Record type: Completed

The cyclin-dependent kinase (CDK) inhibitor **p27**(KIP1) exerts its growth suppressive effects by targeting the cyclin-CDK complexes. Reduced protein levels of **p27** (KIP1) have been reported in numerous human cancers and this has been attributed to increased degradation. However, few reports have addressed the significance of **p27**(KIP1) expression in chemical carcinogenesis of rodents. In a **rat** two-stage urinary bladder carcinogenesis model, with N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) initiation followed by promotion with sodium L-ascorbate (Na-AsA), we evaluated the expression of **p27** (KIP1) protein using immunohistochemistry during various stages of urinary bladder carcinogenesis. In addition, we evaluated the mRNA expression profiles for **p27**(KIP1), **p21** (WAF1/Cip1) and p53 in tumors. Fisher 344 rats were initiated with 0.05% BBN in the drinking water for 4 weeks and then administered 5% Na-AsA in the diet. Immunohistochemical examination revealed **p27** (KIP1) protein to be constitutively expressed in normal urothelium, simple hyperplasia and in most papillary and nodular (PN) hyperplasias and small papillomas, but diminished or absent in large papillomas and in transitional cell carcinomas. An inverse correlation between expression of **p27**(KIP1) and cell proliferation was generally observed. Quantitation of mRNA by multiplex reverse transcription-PCR showed a significant downregulaton of **p27**(KIP1), **p21**(WAF1/Cip1) and p53 mRNA in tumors. More than 50% reduction in **p27**(KIP1) mRNA expression was observed in 42 and 47% of tumors at weeks 18 and 24, respectively; similar reduction in **p21**(WAF1/Cip1) mRNA expression was observed in 58 and 73% of tumors at weeks 18 and 24, and in p53 mRNA expression in 50 and 73% of tumors at weeks 18 and 24, respectively. None of the 25 tumors we examined by PCR-single-strand conformational polymorphism analysis had p53 mutations. These data imply that abnormal down-regulation of **p27**(KIP1), **p21** (WAF1/Cip1) and/or p53 in tumor cells may contribute to the malignant progression of tumors during **rat** two-stage bladder carcinogenesis.

20/3,AB/35 (Item 35 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10237073 99374651 PMID: 10446985

The cell cycle regulator p27kip1 contributes to growth and differentiation of osteoblasts.

Drissi H; Hushka D; Aslam F; Nguyen Q; Buffone E; Koff A; van Wijnen A; Lian JB; Stein JL; Stein GS

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Cancer research (UNITED STATES) Aug 1 **1999**, 59 (15) p3705-11,
ISSN 0008-5472 Journal Code: CNF
Contract/Grant No.: AR39588, AR, NIAMS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

The cyclin-dependent kinase (cdk) inhibitors are key regulators of cell cycle progression. **p27** and **p21** are members of the Cip/Kip family of cdk inhibitors and regulate cell growth by inactivating cell cycle stage-specific CDK-cyclin complexes. Because down-regulation of osteoprogenitor proliferation is a critical step for osteoblast differentiation, we investigated expression of **p27** and **p21** during development of the osteoblast phenotype in **rat** calvarial osteoblasts and in proliferating and growth-inhibited osteosarcoma ROS 17/2.8 cells. Expression of these proteins indicates that **p21**, which predominates in the growth period, is related to proliferation control. **p27** levels are maximal postproliferatively, suggesting a role in the transition from cell proliferation to osteoblast differentiation. We directly examined the role of **p27** during differentiation of osteoprogenitor cells derived from the bone marrow (BM) of **p27**-/-

mice. BM cells from **p27** null mice exhibited increased proliferative activity compared with BM cells from wild-type mice and formed an increased number and larger size of osteoblastic colonies, which further differentiated to the mineralization stage. Although **p27**-/- adherent marrow cells proliferate faster, they retain competency for differentiation, which may result, in part, from observed higher **p21** levels compared with wild type. Histological studies of **p27**-/- bones also showed an increased cellularity in the marrow cavity compared with the **p27** +/+. The increased proliferation in bone does not lead to tumorigenesis, in contrast to observed adenomas in the null mice. Taken together, these findings indicate that **p27** plays a key role in regulating osteoblast differentiation by controlling proliferation-related events in bone cells.

20/3,AB/36 (Item 36 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10234597 99364924 PMID: 10433930
A cell cycle alteration precedes apoptosis of granule cell precursors in the weaver **mouse** cerebellum.
Migheli A; Piva R; Casolino S; Atzori C; Dlouhy SR; Ghetti B
Department of Neuroscience, Laboratory of Neuropathology, University of Turin, Italy.
American journal of pathology (UNITED STATES) Aug **1999**, 155 (2) p365-73, ISSN 0002-9440 Journal Code: 3RS
Contract/Grant No.: PO1 NS 27613, NS, NINDS; RO1 NS14426, NS, NINDS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
A missense mutation in the gene coding for the G-protein-activated inwardly rectifying potassium (GIRK) channel, GIRK2, is responsible for apoptosis in the external germinal layer (EGL) of the cerebellum and a nonapoptotic death of midbrain dopaminergic neurons in the weaver (wv) **mouse**. Failure of axonogenesis and migration are considered to be the primary consequences of GIRK2 channel malfunction in the cerebellum. We investigated whether a disruption of the cell cycle precedes the failure of migration and axonogenesis and leads to massive apoptosis. To this end, immunohistochemistry and immunoblotting for PCNA, Cdk4, cyclin D, cyclin A, and the Cdk inhibitor **p27**/kip1, as well as in situ end-labeling for apoptotic DNA fragmentation, were applied to cerebella of P7-**P21**+/+, wv/+, and wv/wv mice. In +/+ and wv/+ mice, the expression of cell cycle proteins was limited to the outer, premigratory zone of the EGL. Antibodies to **p27** , a marker of cell differentiation, gave a reverse staining pattern. Due to migration delay, patches of **p27**-positive cells persisted in the outer EGL in **P21** wv/+ mice. On the contrary, marked cell cycle up-regulation and absence of **p27** occurred throughout the EGL at all ages in wv/wv mice, indicating an inability to switch off the cell cycle. Mitotic index evaluation showed that cell cycle activation was unrelated to proliferative events. Cell cycle proteins were not expressed in the substantia nigra, suggesting that nonapoptotic death of mature dopaminergic neurons is not preceded by abortive cell cycle re-entry. Our data show that abnormalities of the cell cycle in wv/wv cerebellum represent a major and early consequence of GIRK2 channel malfunction and may strongly influence the susceptibility of EGL cells to apoptosis. These observations may help in understanding the pathogenesis of human neurological channelopathies.

20/3,AB/37 (Item 37 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10232733 99362607 PMID: 10432393
Complement (C5b-9) induces glomerular epithelial cell DNA synthesis but not proliferation in vitro.

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Kidney international (UNITED STATES) Aug **1999**, 56 (2) p538-48, ISSN 0085-2538 Journal Code: KVB
Contract/Grant No.: DK34198, DK, NIDDK; DK47659, DK, NIDDK; DK52121, DK, NIDDK; +
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

BACKGROUND: The C5b-9 membrane attack complex of complement is the principal mediator of injury induced experimentally by antibodies directed at glomerular cell membranes. In experimental membranous nephropathy, C5b-9 induced injury to the glomerular visceral epithelial cell (VEC) is associated with DNA synthesis, but not cytokinesis. In the current study we determined if C5b-9 increases DNA synthesis in VEC in vitro, and defined the mechanisms involved. METHODS: **Rat** VEC in vitro were divided into three groups: (1) sensitized with anti-VEC antibody and exposed to sublytic concentrations of C +/PVG serum (normal complement components); (2) anti-VEC antibody and control C-/PVG serum (C6 deficient); (3) no anti-VEC antibody. DNA synthesis (BrdU staining), mitosis (mitotic figures) and cytokinesis (cell counts) were measured at 24 and 48 hours. To examine the expression of specific S-phase and M-phase cell cycle regulatory proteins and their inhibitors, immunostaining and Western blot analysis was performed for cyclin A, CDK2, **p21** and **p27**, cyclin B and cdc2. RESULTS: In the absence of growth factors, sublytic C5b-9 attack did not increase proliferation. In contrast, sublytic C5b-9 attack (group 1) augmented growth factor induced DNA synthesis by 50% compared to controls (groups 2 and 3; $P < 0.001$), and was accompanied by increased levels of cyclin A and CDK2, and a decrease in the cyclin kinase inhibitor **p27** (but not **p21**). Sublytic C5b-9 attack reduced the expression of the M phase cell cycle proteins, cyclin B and cdc2, accompanied by reduced mitosis (mitotic figures) and cytokinesis (cell number). CONCLUSIONS: Our results show that the C5b-9 augmented growth factor entry into the S phase in VEC is regulated by changes in specific cell cycle regulatory proteins. However, antibody and complement decreased the M phase cell cycle proteins, and prevented VEC mitosis and cytokinesis, suggesting a delay or arrest at the G2/M phase.

20/3,AB/38 (Item 38 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10224833 99340002 PMID: 10409620
Protein kinase Cdelta inhibition of S-phase transition in capillary endothelial cells involves the cyclin-dependent kinase inhibitor **p27** (Kip1).
Ashton AW; Watanabe G; Albanese C; Harrington EO; Ware JA; Pestell RG
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Journal of biological chemistry (UNITED STATES) Jul 23 **1999**, 274 (30) p20805-11, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: CA70897, CA, NCI; CA75503, CA, NCI; HL47032, HL, NHLBI; +
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Distinct protein kinase C (PKC) isoforms differentially regulate cellular proliferation in **rat** microvascular endothelial cells (EC). Overexpression of PKCalpha has little effect on proliferation, whereas PKCdelta slows endothelial cell proliferation and induces S-phase arrest. Analyses were performed on EC overexpressing PKCalpha (PKCalphaEC) or PKCdelta (PKCdeltaEC) to determine the role of specific cell cycle regulatory proteins in the PKCdelta-induced cell cycle arrest. Serum-induced stimulation of cyclins D1, E, and A-associated kinase

activity was delayed by [redacted]2 h in the PKCdeltaEC line in association with S-phase arrest. However, [redacted]e protein levels for cyclins D[redacted]E, and A were similar. Nuclear accumulation of cyclin D1 protein in response to serum was also delayed in PKCdeltaEC. In the PKCdeltaEC line, serum induced **p27** (Kip1) but not p16(Ink4a) or **p21**(Cip1). Serum did not affect **p27** (Kip1) levels in the control vascular endothelial cell line. Immunoprecipitation-Western blotting analysis of **p27**(Kip1) showed serum stimulation of the vascular endothelial cell line resulted in increased amounts of cyclin D1 bound to **p27**(Kip1). In the PKCdeltaEC line, serum did not increase the amount of cyclin D1 bound to **p27** (Kip1). Transfection of full-length **p27** (Kip1) antisense into the PCKdeltaEC line reversed the S-phase arrest and resulted in normal cell cycle progression, suggesting a critical role for **p27**(Kip1) in the PKCdelta-mediated S-phase arrest.

20/3,AB/39 (Item 39 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10210517 99348187 PMID: 10417394
E2F-1 overexpression in cardiomyocytes induces downregulation of p21CIP1 and p27KIP1 and release of active cyclin-dependent kinases in the presence of insulin-like growth factor I.
von Harsdorf R; Hauck L; Mehrhof F; Wegenka U; Cardoso MC; Dietz R
Department of Cardiology, Franz Volhard Clinic, Humboldt University, Berlin, Germany. rhardo@mdc-berlin.de
Circulation research (UNITED STATES) Jul 23 **1999**, 85 (2) p128-36, ISSN 0009-7330 Journal Code: DAJ
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The heart is a postmitotic organ unable to regenerate after injury. The mechanisms controlling cell cycle arrest in cardiomyocytes are still unknown. Adenoviral delivery of E2F-1 to primary **rat** cardiomyocytes resulted in an increase in the expression of key cell cycle activators and apoptosis in >90% of the cells. However, insulin-like growth factor I (IGF-I) rescued cardiomyocytes from E2F-1-induced apoptosis. Furthermore, overexpression of E2F-1 in the presence of IGF-I induced the specific downregulation of total **p21**(CIP1) and **p27**(KIP1) protein levels and their dissociation from cyclin-dependent kinases (cdks). In contrast, p16(INK4) and p57(KIP2) protein levels and their association with cdks remained unaltered. The dissociation of **p21**(CIP1) and **p27**(KIP1) from their cdk complexes correlated well with the activation of cdk2, cdk4, and cdk6 and the release from cell cycle arrest. Under these circumstances, the number of cardiomyocytes in S phase rose from 1.2% to 23%. These results indicate that IGF-I renders cardiomyocytes permissive for cell cycle reentry. Finally, the specific downregulation of **p21**(CIP1) and **p27** (KIP1) further suggests their key role in the maintenance of cell cycle arrest in cardiomyocytes.

20/3,AB/40 (Item 40 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10181150 99262680 PMID: 10329727
sst2 somatostatin receptor mediates cell cycle arrest and induction of **p27**(Kip1). Evidence for the role of SHP-1.
Pages P; Benali N; Saint-Laurent N; Esteve JP; Schally AV; Tkaczuk J; Vaysse N; Susini C; Buscail L
INSERM U 151, Institut Louis Bugnard, CHU Rangueil, F 31403 Toulouse Cedex, France.
Journal of biological chemistry (UNITED STATES) May 21 **1999**, 274 (21) p15186-93, ISSN 0021-9258 Journal Code: HIV
Languages: ENGLISH
Document type: Journal Article

Record type: Completed

Activation of the somatostatin receptor sst2 inhibits cell proliferation by a mechanism involving the stimulation of the protein-tyrosine phosphatase SHP-1. The cell cycle regulatory events leading to sst2-mediated growth arrest are not known. Here, we report that treatment of Chinese hamster ovary cells expressing sst2 with the somatostatin analogue, RC-160, led to G1 cell cycle arrest and inhibition of insulin-induced S-phase entry through induction of the cyclin-dependent kinase inhibitor **p27**(Kip1). Consequently, a decrease of **p27** (Kip1)-cdk2 association, an inhibition of insulin-induced cyclin E-cdk2 kinase activity, and an accumulation of hypophosphorylated retinoblastoma gene product (Rb) were observed. However, RC-160 had no effect on the **p21** (Waf1/Cip1). When sst2 was coexpressed with a catalytically inactive mutant SHP-1 in Chinese hamster ovary cells, mutant SHP-1 induced entry into cell cycle and down-regulation of **p27**(Kip1) and prevented modulation by insulin and RC-160 of **p27**(Kip1) expression, **p27** (Kip1)-cdk2 association, cyclin E-cdk2 kinase activity, and the phosphorylation state of Rb. In **mouse** pancreatic acini, RC-160 reverted down-regulation of **p27**(Kip1) induced by a mitogen, and this effect did not occur in acini from viable motheaten (mev/mev) mice expressing a mutant SHP-1 with markedly deficient enzymes. These findings provide the first evidence that sst2 induces cell cycle arrest through the up-regulation of **p27**(Kip1) and demonstrate that SHP-1 is required for maintaining high inhibitory levels of **p27**(Kip1) and is a critical target of the insulin, and somatostatin signaling cascade, leading to the modulation of **p27**(Kip1).

20/3,AB/41 (Item 41 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10168438 99289199 PMID: 10362353

Evidence for a p23 caspase-cleaved form of **p27**[KIP1] involved in G1 growth arrest.

Loubat A; Rochet N; Turchi L; Rezzonico R; Far DF; Auberger P; Rossi B; Ponzio G

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Oncogene (ENGLAND) Jun 3 **1999**, 18 (22) p3324-33, ISSN 0950-9232 Journal Code: ONC

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

p27[KIP1] (**p27**) is a cyclin dependent kinase inhibitor, involved in the negative regulation of G1 progression in response to a number of anti-proliferative signals. In this study we show, in growing **mouse** hybridoma (7TD1) and human myeloma (U266) cell lines, that **p27** is highly expressed but slightly upregulated when cells are arrested, regardless to the phases of the cell cycle. In contrast, the specific blockade of these cells in early G1 phase reveals the induction of a protein of 23 kDa (p23) specifically recognized by polyclonal anti-**p27** antibodies raised against the NH2 terminal part of **p27** but not by anti-**p21** [CIP1] antibodies. Experiments using caspase inhibitors strongly suggest that p23 results from the proteolysis of **p27** by a 'caspase-3-like' protease. This cleavage leads to the cytosolic sequestration of p23 but does not alter its binding properties to CDK2 and CDK4 kinases. Indeed, p23 associated in vivo with high molecular weight complexes and coprecipitated with CDK2 and CDK4. We demonstrate by transfection experiments in SaOS-2 cells that p23 induces a G1 phase growth arrest by inhibition of cyclin/CDK2 activity. In summary we describe here a caspase-cleaved form of **p27** , induced in absence of detectable apoptosis and likely involved in cell cycle regulation.

20/3,AB/42 (Item 42 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

10164999 99269839 PMID: 10337545
Cyclin-dependent kinase inhibitor expression in human heart failure. A comparison with fetal development.
Burton PB; Yacoub MH; Barton PJ
Imperial College of School of Medicine, National Heart and Lung Institute, London, U.K.
European heart journal (ENGLAND) Apr **1999**, 20 (8) p604-11, ISSN 0195-668X Journal Code: EM8
Comment in Eur Heart J. 1999 Apr;20(8) 555-7
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
AIMS: Terminal differentiation of cardiac myocyte is associated with their permanent withdrawal from the cell cycle. In adult end-stage heart failure, significant numbers of myocytes express proliferating cell nuclear antigen yet fail to progress to cell division. Cyclin dependent kinase inhibitors are powerful inhibitors of the cell cycle and may play a direct role both in myocyte development and in preventing cell division in the adult. METHODS AND RESULTS: The expression of the CIP/KIP cyclin dependent kinase inhibitors **p21**, **p27**, p57 and the retinoblastoma protein was examined in acute (seen in brain dead transplant donors) and end-stage heart failure by Western blot analysis and compared to that seen in human and **rat** cardiac development. The expression of **p21** showed a gradual increase during development in both **rat** and man, becoming maximal in adulthood **p27** . levels showed an initial rise with subsequent continual expression throughout life. p57 expression was detectable at only early stages in **rat** but persisted throughout life in man. In both acute and end-stage heart failure the levels of **p21**, **p27** and p57 reverted to a pattern similar to that observed in human fetal heart: **p21** and **p27** declined while p57 expression was significantly increased. In contrast, retinoblast protein levels declined during human heart development but were unaltered in heart failure. CONCLUSIONS: The expression of **p21**, but not **p27** or p57, is consistent with a role in the gradual withdrawal of cardiac myocytes from cell cycle during development. In adult heart failure cyclin dependent kinase inhibitor expression reverts to the fetal pattern but is insufficient to initiate cell cycle activation.

20/3,AB/43 (Item 43 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10125960 99177171 PMID: 10075928
The **p21**(Cip1) and **p27**(Kip1) CDK 'inhibitors' are essential activators of cyclin D-dependent kinases in murine fibroblasts.
Cheng M; Olivier P; Diehl JA; Fero M; Roussel MF; Roberts JM; Sherr CJ
Department of Tumor Cell Biology, St Jude Children's Research Hospital, 332 N. Lauderdale, Memphis, TN 38105, USA.
EMBO journal (ENGLAND) Mar 15 **1999**, 18 (6) p1571-83, ISSN 0261-4189 Journal Code: EMB
Contract/Grant No.: CA-21765, CA, NCI; CA-56819, CA, NCI; T32-CA-70089, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The widely prevailing view that the cyclin-dependent kinase inhibitors (CKIs) are solely negative regulators of cyclin-dependent kinases (CDKs) is challenged here by observations that normal up-regulation of cyclin D- CDK4 in mitogen-stimulated fibroblasts depends redundantly upon **p21**(Cip1) and **p27**(Kip1). Primary **mouse** embryonic fibroblasts that lack genes encoding both **p21** and **p27** fail to assemble detectable amounts of cyclin D-CDK complexes, express cyclin D proteins at much reduced levels, and are unable to efficiently direct cyclin D proteins to

the cell nucleus. Restoration of CKI function reverses all three defects and thereby restores cyclin D activity to normal physiological levels. In the absence of both CKIs, the severe reduction in cyclin D-dependent kinase activity was well tolerated and had no overt effects on the cell cycle.

20/3,AB/44 (Item 44 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10036919 99145409 PMID: 10022811
Activation of telomerase and its association with G1-phase of the cell cycle during UVB-induced skin tumorigenesis in SKH-1 hairless **mouse**.
Balasubramanian S; Kim KH; Ahmad N; Mukhtar H
Department of Dermatology, Case Western Reserve University, Cleveland, Ohio 44106, USA.
Oncogene (ENGLAND) Feb 11 **1999**, 18 (6) p1297-302, ISSN 0950-9232 Journal Code: ONC
Contract/Grant No.: P01 CA 48735, CA, NCI; P30 CA 43703, CA, NCI; R01 CA 51802, CA, NCI; +
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Telomerase is a ribonucleoprotein enzyme that adds hexanucleotide repeats TTAGGG to the ends of chromosomes. Telomerase activation is known to play a crucial role in cell-immortalization and carcinogenesis. Telomerase is shown to have a correlation with cell cycle progression, which is controlled by the regulation of cyclins, cyclin dependent kinases (cdks) and cyclin dependent kinase inhibitors (cdkis). Abnormal expression of these regulatory molecules may cause alterations in cell cycle with uncontrolled cell growth, a universal feature of neoplasia. Skin cancer is the most prevalent form of cancer in humans and the solar UV radiation is its major cause. Here, we investigated modulation in telomerase activity and protein expression of cell cycle regulatory molecules during the development of UVB-induced tumors in SKH-1 hairless mice. The mice were exposed to 180 mjoules/cm2 UVB radiation, thrice weekly for 24 weeks. The animals were sacrificed at 4 week intervals and the studies were performed in epidermis. Telomerase activity was barely detectable in the epidermis of non-irradiated **mouse**. UVB exposure resulted in a progressive increase in telomerase activity starting from the 4th week of exposure. The increased telomerase activity either persisted or further increased with the increased exposure. In papillomas and carcinomas the enzyme activity was comparable and was 45-fold higher than in the epidermis of control mice. Western blot analysis showed an upregulation in the protein expression of cyclin D1 and cyclin E and their regulatory subunits cdk4 and cdk2 during the course of UVB exposure and in papillomas and carcinomas. The protein expression of cdk6 and ckis viz. p16/Ink4A, **p21**/Waf1 and **p27**/Kip1 did not show any significant change in UVB exposed skin, but significant upregulation was observed both in papillomas and carcinomas. The results suggest that telomerase activation may be involved in UVB-induced tumorigenesis in **mouse** skin and that increased telomerase activity may be associated with G1 phase of the cell cycle.

20/3,AB/45 (Item 45 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09981855 99057884 PMID: 9837900
Calmodulin is essential for cyclin-dependent kinase 4 (Cdk4) activity and nuclear accumulation of cyclin D1-Cdk4 during G1.
Taules M; Rius E; Talaya D; Lopez-Girona A; Bachs O; Agell N
Department of Cell Biology, Institut d'Investigacions Biomediques August Pi i Sunyer, Faculty of Medicine, University of Barcelona, Casanova 143, 08036 Barcelona, Spain.
Journal of biological chemistry (UNITED STATES) Dec 11 **1998**, 273 (50) p33279-86, ISSN 0021-9258 Journal Code: HIV

Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Although it is known that calmodulin is involved in G1 progression, the calmodulin-dependent G1 events are not well understood. We have analyzed here the role of calmodulin in the activity, the expression, and the intracellular location of proteins involved in G1 progression. The addition of anti-calmodulin drugs to normal **rat** kidney cells in early G1 inhibited cyclin-dependent kinase 4 (Cdk4) and Cdk2 activities, as well as retinoblastoma protein phosphorylation. Protein levels of cdk4, cyclin D1, cyclin D2, cyclin E, **p21**, and **p27** were not affected after CaM inhibition, whereas decreases in the amount of cyclin A and Cdc2 were observed. The decrease of Cdk4 activity was due neither to changes in its association to cyclin D1 nor to changes in the amount of **p21** or **p27** bound to cyclin D1-Cdk4 complexes. Calmodulin inhibition also produced a translocation of nuclear cyclin D1 and Cdk4 to the cytoplasm. This translocation could be responsible for the decreased Cdk4 activity upon calmodulin inhibition. Immunoprecipitation, calmodulin affinity chromatography, and direct binding experiments indicated that calmodulin associates with Cdk4 and cyclin D1 through a calmodulin-binding protein. The facts that Hsp90 interacts with Cdk4 and that its inhibition induced Cdk4 and cyclin D1 translocation to the cytoplasm point to Hsp90 as a good candidate for being the calmodulin-binding protein involved in the nuclear accumulation of Cdk4 and cyclin D1.

20/3,AB/46 (Item 46 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09954750 99054662 PMID: 9840927
Cyclin E2: a novel CDK2 partner in the late G1 and S phases of the mammalian cell cycle.
Lauper N; Beck AR; Cariou S; Richman L; Hofmann K; Reith W; Slingerland JM; Amati B
Swiss Institute for Experimental Cancer Research (ISREC), Epalinges.
Oncogene (ENGLAND) Nov 19 **1998**, 17 (20) p2637-43, ISSN 0950-9232 Journal Code: ONC
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

We report here the cloning and characterization of human and **mouse** cyclin E2, which define a new subfamily within the vertebrate E-type cyclins, while all previously identified family-members belong to the cyclin E1 subfamily. Cyclin E2/CKD2 and cyclin E/CDK2 complexes phosphorylate histone H1 in vitro with similar specific activities and both are inhibited by p27Kip1. Cyclin E2 mRNA levels in human cells oscillate throughout the cell cycle and peak at the G1/S boundary, in parallel with the cyclin E mRNA. In cells, cyclin E2 is complexed with CDK2, **p27** and **p21**. Like cyclin E, cyclin E2 is an unstable protein in vivo and is stabilized by proteasome inhibitors. Cyclin E2-associated kinase activity rises in late G1 and peaks very close to cyclin E activity. In two malignantly transformed cell lines, cyclin E2 activity is sustained throughout S phase, while cyclin E activity has already declined and cyclin A activity is only beginning to rise. We speculate that cyclin E2 is not simply redundant with cyclin E, but may regulate distinct rate-limiting pathway(s) in G1-S control.

20/3,AB/47 (Item 47 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09933969 99009264 PMID: 9790949
Genistein induces **p21**(Cip1/WAF1) expression and blocks the G1 to S phase transition in **mouse** fibroblast and melanoma cells.
Kuzumaki T; Kobayashi T; Ishikawa K

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Biochemical and biophysical research communications (UNITED STATES) Oct 9 **1998**, 251 (1) p291-5, ISSN 0006-291X Journal Code: 9Y8
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Genistein, the principal isoflavonoid in soybeans, is reported to inhibit cell cycle progression, but the molecular basis for this event is unknown. Here we show that genistein inhibits DNA synthesis and suppresses cyclin E-associated cyclin-dependent kinase-2 (CDK2) activity when quiescent BALB/c 3T3 fibroblasts are stimulated with serum. In these cells, a CDK2 inhibitor, **p21** (Cip1/WAF1), is markedly increased by genistein, but another CDK2 inhibitor, **p27**(Kip1), is not increased. In exponentially growing BALB/c 3T3 cells, genistein inhibits proliferation of the cells in a dose-dependent manner. Flow cytometric analysis and measurement of DNA synthesis indicate that genistein blocks the G1 to S phase transition of these cells, which is concomitant with G2-M arrest. In **mouse** B16-F1 melanoma cells, genistein also blocks the transition of G1 to S phase without arresting at G2-M at low doses. In both cell lines, genistein suppresses cyclin E/CDK2 activity and induces **p21** (Cip1/WAF1) expression. These results suggest that genistein affects the restriction point control of the cell cycle by inducing **p21**(Cip1/WAF1) expression in **mouse** fibroblast and melanoma cells. Copyright 1998 Academic Press.

20/3,AB/48 (Item 48 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09924385 98435855 PMID: 9764826
Early G1 growth arrest of hybridoma B cells by DMSO involves cyclin D2 inhibition and **p21**[CIP1] induction.
Ponzio G; Loubat A; Rochet N; Turchi L; Rezzonico R; Farahi Far D; Dulic V; Rossi B
INSERM U364, Faculte de Medecine, Nice, France.
Oncogene (ENGLAND) Sep 3 **1998**, 17 (9) p1159-66, ISSN 0950-9232 Journal Code: ONC
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Dimethylsulfoxide (DMSO) was shown to inhibit the proliferation of several B cell lines including Raji, Daudi, and SKW6-CL4 but the mechanisms involved in this growth arrest are still unclear. We show that in 7TD1 **mouse** hybridoma cells a DMSO-induced reversible G1 arrest involves inactivation of Rb kinases, cyclin D2/CDK4 and cyclin E/CDK2. This occurs by at least three distinct mechanisms. Inhibition of cyclin D2 neosynthesis leads to a dramatic decrease of cyclinD2/CDK4 complexes. This in turn enables the redistribution of **p27**[KIP1] from cyclin D2/CDK4 to cyclin E/CDK2 complexes. In addition, the simultaneous accumulation of **p21** [CIP1] entails increasing association with cyclin D3/CDK4 and cyclin E/CDK2. Thus, **p21**[CIP1] and **p27** [KIP1], act in concert to inhibit cyclin E/CDK2 activity which, together with CDK4 inactivation, confers a G1-phase arrest.

20/3,AB/49 (Item 49 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09901372 98380034 PMID: 9716177
Regulation of cyclin-dependent kinase 4 during adipogenesis involves switching of cyclin D subunits and concurrent binding of p18INK4c and p27Kip1.
Phelps DE; Xiong Y
Lineberger Comprehensive Cancer Center, University of North Carolina at

Chapel Hill, 27599, USA.
Cell growth & differen[redacted]ion (UNITED STATES) Aug **1998**[redacted]9 (8) p595-610, ISSN 1044-9523 Journal Code: AYH
Contract/Grant No.: 1F32GM18437-01, GM, NIGMS; CA-68377, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Terminal differentiation of many cell lineages involves an exit from the mitotic cycle and entry into, and maintenance of, a permanent state of G1 arrest. We found that during terminal differentiation of **mouse** 3T3-L1 preadipocytes, the level of cyclin-dependent kinase 4 (CDK4) remained constant, but the subunit composition of the CDK4 complex underwent a dynamic rearrangement. As 3T3-L1 cells differentiated, the levels of cyclin D1 and cyclin D1-CDK4 complexes declined to negligible levels. Meanwhile, cyclins D2 and D3 levels and their associations with CDK4 increased transiently and persistently, respectively, with cyclin D3 becoming the predominant cyclin partner of CDK4 in mature adipocytes. At least five CDK inhibitors are expressed during the differentiation program of 3T3-L1 cells. Both p15INK4b and p16INK4a continuously declined to undetectable levels immediately after differentiation induction. **p21** was transiently expressed during the exit of 3T3-L1 cells from mitotic clonal expansion and then decreased to undetectable levels in mature adipocytes. The level of p27KiP1 and **p27** -CDK4 complexes remain high during differentiation and in mature adipocytes. Distinctly, there is a remarkable induction of p18INK4c mRNA and protein that was not seen in the closely related nondifferentiating 3T3-C2 cell line, suggesting that p18 induction in 3T3-L1 cells is related to cell differentiation, not cell cycle arrest. The pRb kinase activity of cyclin D3 and CDK4 was not detected in quiescent 3T3-L1 cells and was then induced as the cells entered the mitotic clonal expansion phase. Unexpectedly, cyclin D3 and CDK4 pRb kinase activity remained high after 3T3-L1 cells completed their mitotic division and was still readily detectable in mature adipocytes. Our study reveals an active regulation, rather than passive inhibition, of CDK4 activity during adipocyte differentiation. Two central features of this complex regulation are switching of activating cyclin D subunits and concurrent binding by the p18 and **p27** CDK inhibitors.

20/3,AB/50 (Item 50 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09891229 98358657 PMID: 9693786
Regulation of cyclin dependent kinase inhibitor proteins during neonatal cerebella development.
Watanabe G; Pena P; Shambaugh GE; Haines GK; Pestell RG
Albert Einstein Cancer Center, Department of Medicine, Bronx, NY 10461, USA.
Brain research. Developmental brain research (NETHERLANDS) Jun 15 **1998**, 108 (1-2) p77-87, ISSN 0165-3806 Journal Code: DBR
Contract/Grant No.: 1R29CA70897, CA, NCI; 5-P30-CA13330-26, CA, NCI; R55CA75503, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The cyclin dependent kinase holoenzymes (CDKs), composed of catalytic (cdk) and regulatory (cyclin) subunits, promote cellular proliferation and are inhibited by cyclin dependent kinase inhibitor proteins (CDKIs). The CDKIs include the Ink4 family (p15Ink4b, p16Ink4a, p18Ink4c, p19Ink4d) and the KIP family (p21Cip1 and p27Kip1). The sustained induction of **p21** and p18 during myogenesis implicates these CDKI in maintaining cellular differentiation. Herein we examined the CDK (cyclin D1, cdk5) and CDKI expression profiles during the first 24 days of postnatal **rat** cerebella development. Cdk5 abundance increased and cyclin D1 decreased from day 9 through to adulthood. The CDKIs increased transiently during differentiation. **p27** increased 20-fold between days 4 and 24, whereas

p21 rose twofold between 6 to 11 days. p19, p18 and p16 increased approximately two- to threefold, falling to low levels in the adult. Immunostaining of cyclin D1 was localized in the external granular cells, whereas **p27**, was found primarily in the Purkinje cells. The period of maximal differentiation between days 9 to 13 was associated with a change in **p21** and p16 staining from the external granular and Purkinje cells to a primarily Purkinje cell distribution. Protein-calorie malnutrition, which was previously shown to arrest **rat** cerebella development, reduced cyclin D1 kinase activity and **p27** levels. However, p16 and **p21** levels were unchanged. We conclude that the CDKIs are induced with distinct kinetics in specific cell types and respond differentially to growth factors during cerebella development, suggesting discrete roles for these proteins in normal cerebella development.

20/3,AB/51 (Item 51 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09826194 98284301 PMID: 9621281
The cyclin kinase inhibitor p21WAF1, CIP1 is increased in experimental diabetic nephropathy: potential role in glomerular hypertrophy.
Kuan CJ; al-Douahji M; Shankland SJ
Division of Nephrology, University of Washington Medical Center, Seattle 98195, USA.
Journal of the American Society of Nephrology (UNITED STATES) Jun **1998**, 9 (6) p986-93, ISSN 1046-6673 Journal Code: A6H
Contract/Grant No.: DK51096, DK, NIDDK; DK52121, DK, NIDDK
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
High glucose inhibits mesangial cell proliferation in vitro and induces hypertrophy in mesangial cells in culture and in experimental diabetic nephropathy. Cell growth is ultimately controlled at the level of the cell cycle by cell cycle regulatory proteins. Cell cycle progression requires that cyclin-dependent kinases be activated by cyclins. Cyclin kinase inhibitors (CKI) inactivate cyclin-dependent kinases, causing cell cycle arrest. In the current study, high glucose-induced mesangial cell hypertrophy in vitro is shown to be associated with increased levels of the CKI **p21**, but not **p27** . In the streptozotocin model of experimental diabetes in the **mouse** , glomerular hypertrophy was associated with a selective increase in **p21** expression, whereas the levels of the CKI **p27** and p57 did not change. Unlike many other forms of glomerular injury, diabetic nephropathy was not associated with increased apoptosis. These results support a role for **p21** in causing glomerular cell hypertrophy in diabetic nephropathy.

20/3,AB/52 (Item 52 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09817360 98337899 PMID: 9671688
Optimal effectiveness of BDNF for fetal nigral transplants coincides with the ontogenic appearance of BDNF in the striatum.
Yurek DM; Hipkens SB; Wiegand SJ; Altar CA
Department of Surgery/Neurosurgery and Anatomy and Neurobiology, University of Kentucky College of Medicine, Lexington, Kentucky 40536, USA.
Journal of neuroscience (UNITED STATES) Aug 1 **1998**, 18 (15) p6040-7, ISSN 0270-6474 Journal Code: JDF
Contract/Grant No.: NS29994, NS, NINDS; NS35890, NS, NINDS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Transplantation of fetal nigral dopamine neurons into the caudate and putamen of Parkinson's disease patients produces limited symptomatic relief. One approach to augment the outgrowth and function of nigral grafts

includes exposure of the [redacted]raphs to neurotrophic factors; however, the temporal requirements for op[redacted]izing these actions are unknow[redacted] The present study characterized the ontogeny of brain-derived neurotrophic factor (BDNF) in the **rat** striatum and used this information to define and evaluate three distinct periods of BDNF infusion into fetal nigral grafts transplanted into the striatum of rats with experimental Parkinson's disease. At postnatal day 1 (P1), BDNF and dopamine were measured at 17 and 27% of peak levels, respectively, that occurred at **P27** for both. Both compounds showed their greatest surge between P7 and P20, increasing from 40% to approximately 95% of peak levels. Exogenous BDNF infused into transplants during weeks 1 and 2 after the transplantation, which coincide with the developmental period embryonic day 14 (E14)-P7 for transplanted tissue, did not improve rotational behavior or enhance fiber outgrowth of transplanted dopamine neurons. Delaying the BDNF infusion until transplanted tissue was approximately P8-**P21** greatly enhanced the effect on rotational behavior and doubled the area of dopamine fiber outgrowth from the transplants. Delaying the infusion until transplanted tissue was approximately P36-P49 failed to augment fiber outgrowth and decreased the behavioral function of transplants. Thus, the optimal effect of exogenous BDNF on the development of dopamine neurons in fetal nigral transplants occurs at a postnatal age when endogenous dopamine and BDNF show the greatest increases during the normal development of the striatum.

20/3,AB/53 (Item 53 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09731250 98204760 PMID: 9535785
Regulation of cyclin D-dependent kinase activity in **rat** liver regeneration.
Kato A; Ota S; Bamba H; Wong RM; Ohmura E; Imai Y; Matsuzaki F
1st Department of Internal Medicine, Saitama Medical Center, Saitama Medical School, 1981 Tsujido, Kamoda, Saitama, Kawagoe, 350-8550, Japan.
Biochemical and biophysical research communications (UNITED STATES) Apr 7 **1998**, 245 (1) p70-4, ISSN 0006-291X Journal Code: 9Y8
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The regulation of cyclin D-dependent kinase activity in tissue regeneration in vivo has not been fully described. In young adult **rat** liver after 70% partial hepatectomy, the association of cyclin D1 with cdk4 was significantly promoted during G1 phase and was maximal at 18 hr, corresponding mainly to late G1. Cyclin D1-dependent kinase activity also strongly increased during G1 phase. The timing of the induction of cyclin D1 / cdk4 complex assembly correlated well with that of cyclin D1-dependent kinase activity. At 18 hr after partial hepatectomy, the amounts of CDK inhibitors **p21**(CIP1) and **p27** (KIP1) were also maximal, while only one-tenth of **p21**(CIP1) and of **p27**(KIP1) was associated with cyclin D1. These findings suggest that cyclin D1, cdk4 and their association act as promoting factors, and that both **p21**(CIP1) and **p27** (KIP1) may have physiological functions as adaptor proteins in additions to their roles as CDK inhibitors in **rat** liver regeneration.

20/3,AB/54 (Item 54 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09721173 98182413 PMID: 9515024
Persistent and heterogenous expression of the cyclin-dependent kinase inhibitor, p27KIP1, in **rat** hearts during development.
Koh KN; Kang MJ; Frith-Terhune A; Park SK; Kim I; Lee CO; Koh GY
Department of Physiology and Institute of Cardiovascular Research, Chonbuk National University Medical School, Chonju, 560-180, Republic of Korea.

Journal of molecular and cellular cardiology (ENGLAND) Mar 1998, 30 (3) p463-74, ISSN 0022-2828 Journal Code: J72
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

We have previously shown that there were differential and dramatic decreases of cyclin and cyclin-dependent kinase (CDK) activities in cardiomyocytes during the neonatal period. The activity of CDKs control cell cycle progression, and this activity is regulated positively and negatively by association of CDKs with cyclins and cyclin-dependent kinase inhibitors (CKIs), respectively. While the INK family (p15(INK4B)/p16(INK4A)/p18(INK4C)/p19(INK4D)) of CKIs is not detectable in hearts, the KIP/CIP family (**p21**(CIP1), **p27**(KIP1) and p57(KIP2)) of CKIs is detectable in most organs including the heart. Differential and dramatic changes of the KIP/CIP family (**p21**(CIP1), **p27**(KIP1) and p57(KIP2)) of CKIs were detected in **rat** hearts during development. The mRNA and protein levels of **p21**(CIP1) and p57(KIP2) were readily detectable in hearts at gestational and early postnatal periods and decreased thereafter. The mRNA levels of **p27**(KIP1) in ventricles were high during the gestational period, and did not change until day 30 postnatal, then were decreased slightly in 90-day-old rats. The protein levels of **p27**(KIP1) increased significantly in the early postnatal period, then were expressed persistently, although levels decreased slightly in the adult period. However, protein levels of **p27** (KIP1) in atria did not change during development. Variable immuno-staining patterns of **p27** (KIP1) were observed at different periods of development and in various locations in myocardium. During the gestational period, approximately 35-50% of myocardial cells in the cardiac wall were **p27**(KIP1) immuno-positive and were distributed diffusely. These **p27** (KIP1) immunopositive cells increased predominantly in endocardial and mid-portion areas of ventricular myocardium at the early postnatal period. This heterogenous pattern of **p27**(KIP1) protein expression persisted to adult hearts though the percentage of **p27** (KIP1) immuno-positive cells decreased slightly. High magnification revealed that more than 50% of adult cardiomyocytes were **p27**(KIP1) immuno-positive and that **p27** (KIP1) was located solely in nuclei. These results indicate that **p27**(KIP1) may be an important inhibitor of CDK activities in cardiomyocytes during early postnatal development and may block the re-entrance of adult cardiomyocytes into the cell cycle after injury.

20/3,AB/55 (Item 55 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09689983 98162605 PMID: 9500999
Alterations in cell cycle regulation in **mouse** skin tumors.
Balasubramanian S; Ahmad N; Jeedigunta S; Mukhtar H
Department of Dermatology, Case Western Reserve University, Cleveland, Ohio 44106, USA.
Biochemical and biophysical research communications (UNITED STATES) Feb 24 **1998**, 243 (3) p744-8, ISSN 0006-291X Journal Code: 9Y8
Contract/Grant No.: AR 39750, AR, NIAMS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

The connection between cell cycle and cancer has become obvious in as much as it is considered that dysregulated cellular proliferation is a hallmark of cancer. In many studies, the dysregulation of the cyclin-cdk-cki network has been reported in experimental animal and human tumors, but to our knowledge a complete profile of alterations in regulatory molecules in any tumor model system is lacking. In this study, we assessed the expression of various cyclins, cyclin dependent kinases, and cyclin kinase inhibitors in chemically induced squamous papillomas in SENCAR **mouse** skin. Western blot analysis data showed a significant

upregulation of cyclins (3[redacted] 6, 19, and 12 folds elevation for cyclin-D1, D2, E, and A, respectiv[redacted] in tumors compared to the n[redacted]al skin. The protein expression of the cdk (1, 2, and 4) was also found to be elevated in tumors compared to normal skin (33 fold for cdk1, 14 fold for cdk2, and 9 fold for cdk4). In tumors, compared to the normal skin, a significant increase in the level of protein expression of **p27** and p57 (4 and 3 fold, respectively) was evident. In normal skin, p16 and **p21** were not detectable but significant expression of these proteins was detected in tumors. Taken together, these data provide evidence that cell cycle deregulation in G1-phase is a critical event during the course of two stage skin carcinogenesis. This may have relevance to epithelial cancers in general.

20/3,AB/56 (Item 56 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09659928 98113158 PMID: 9442036
Glucocorticoids stimulate **p21** gene expression by targeting multiple transcriptional elements within a steroid responsive region of the p21waf1/cip1 promoter in **rat** hepatoma cells.
Cha HH; Cram EJ; Wang EC; Huang AJ; Kasler HG; Firestone GL
Department of Molecular and Cell Biology, University of California, Berkeley 94720, USA.
Journal of biological chemistry (UNITED STATES) Jan 23 **1998**, 273 (4) p1998-2007, ISSN 0021-9258 Journal Code: HIV
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Glucocorticoids can induce a G1 arrest in the cell cycle progression of BDS1 **rat** hepatoma cells. In these cells, dexamethasone, a synthetic glucocorticoid, stimulated a rapid and selective increase in expression of the **p21** cyclin-dependent kinase (CDK) inhibitor mRNA and protein and virtually abolished CDK2 phosphorylation of the retinoblastoma protein. Expression of the **p27** CDK inhibitor, and other G1-acting cell cycle proteins, remained unaffected. Dexamethasone stimulated **p21** promoter activity in a p53-independent manner that required functional glucocorticoid receptors. Transforming growth factor-beta, which also induced a G1 cell cycle arrest of the hepatoma cells, failed to elicit this response. Analysis of 5' deletions of the **p21** promoter uncovered a glucocorticoid responsive region between nucleotides -1481 and -1184, which does not contain a canonical glucocorticoid response element but which can confer dexamethasone responsiveness to a heterologous promoter. Fine mapping of this region uncovered three distinct 50-60-base pair transcriptional elements that likely function as targets of glucocorticoid receptor signaling. Finally, ectopic expression of **p21** had no effect on hepatoma cell growth in the absence of glucocorticoids but facilitated the ability of dexamethasone to inhibit cell proliferation. Thus, our results have established a direct transcriptional link between glucocorticoid receptor signaling and the regulated promoter activity of a CDK inhibitor gene that is involved in the cell cycle arrest of hepatoma cells.

20/3,AB/57 (Item 57 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09636316 98099220 PMID: 9438383
p27Kip1 is expressed transiently in developing myotomes and enhances myogenesis.
Zabludoff SD; Csete M; Wagner R; Yu X; Wold BJ
Division of Biology, California Institute of Technology, Pasadena 91125, USA.
Cell growth & differentiation (UNITED STATES) Jan **1998**, 9 (1) p1-11, ISSN 1044-9523 Journal Code: AYH

Contract/Grant No.: AR40703, AR, NIAMS; AR42671, AR, NIAMS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Vertebrate skeletal muscle development is characterized by tight coupling of muscle differentiation with cell cycle arrest in G1/G0. Key regulators of G1 progression are the G1 cyclin-dependent kinases, their positive regulators, the G1 cyclins, and their negative regulators, the cyclin-dependent kinase inhibitors (CDIs). Here we show that p27Kip1 protein, a G1 CDI, is expressed in a prominent but transient wave in the developing myotomes of the **mouse** embryo. We relate its expression to expression of MyoD and myogenin proteins, which are determination and differentiation class myogenic regulatory factors, respectively. Functional assays showed that ectopic **p27** expression can powerfully enhance the efficiency of MyoD-initiated muscle differentiation in cell culture. When considered together with the myotomal expression patterns of p18, **p21**, and p57, these results suggest a model in which **p27** acts as a "trigger" CDI while myoblasts are exiting the cell cycle and initiating differentiation. At later times, when **p27** protein has been down-regulated, it is proposed that accumulation of p18, **p21**, and p57 maintain the differentiated myocytes in a postmitotic state.

20/3,AB/58 (Item 58 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09598954 98060570 PMID: 9399649
Malignant transformation by cyclin E and Ha-Ras correlates with lower sensitivity towards induction of cell death but requires functional Myc and CDK4.
Haas K; Johannes C; Geisen C; Schmidt T; Karsunky H; Blass-Kampmann S; Obe G; Moroy T
Institut fur Zellbiologie (Tumorforschung), I F Z, Universitatsklinikum Essen, Germany.
Oncogene (ENGLAND) Nov 20 **1997**, 15 (21) p2615-23, ISSN 0950-9232 Journal Code: ONC
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
We demonstrate in this paper that the G1 phase specific cell cycle regulator cyclin E is able to provoke focus formation when cotransfected with activated Ha-ras into primary **rat** embryo fibroblasts (REFs). Cyclin E/Ha-ras transformed cells are highly tumorigenic in synergeneic rats, are able to form colonies in soft agar and show protection towards apoptosis upon serum starvation or DNA damage compared to cells transformed by the combination of Myc, cyclin D1 or SV40 large T-antigen and Ha-ras. Lines that were established after cyclin E/Ha-ras or cyclin D1/Ha-ras transformation contain a large percentage of polyploid cells. This was not observed in cells transformed with other oncoproteins and Ha-ras pointing to an involvement of D- and E type cyclins in genomic instability. The cyclin dependent kinase inhibitors **p21** and **p27** but also p16 completely abrogate focus formation by cyclin E and Ha-ras suggesting that the oncogenic activity of cyclin E still requires functional G1 specific cyclin/CDK complexes. Moreover, inhibition of Myc function also blocks the oncogenic activity of cyclin E indicating a requirement of Myc for cyclin E function. The findings presented here demonstrate that cyclin E can act as an oncoprotein with a potential involvement in genomic instability and the prevention of cell death. Our data also present more evidence for a strict functional interdependency between G1 cyclin/CDK complexes and c-Myc.

20/3,AB/59 (Item 59 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09595475 97463042 PMID: 9321826

Downregulation of cyclin-dependent kinase inhibitors p21 and **p27** in pressure-overload hypertrophy.
Li JM; Brooks G
Rayne Institute, St. Thomas' Hospital, London, United Kingdom.
American journal of physiology (UNITED STATES) Sep **1997**, 273 (3 Pt 2) pH1358-67, ISSN 0002-9513 Journal Code: 3U8
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
We postulated that the cyclin-dependent kinase inhibitors **p21** and **p27** could regulate the alterations in growth potential of cardiomyocytes during left ventricular hypertrophy (LVH). LVH was induced in adult **rat** hearts by aortic constriction (AC) and was monitored at days 0, 1, 3, 7, 14, 21, and 42 postoperation. Relative to sham-operated controls (SH), left ventricle (LV) weight-to-body weight ratio in AC increased progressively with time without significant differences in body weight or right ventricle weight-to-body weight ratio. Atrial natriuretic factor mRNA increased significantly in AC to 287% at day 42 compared with SH ($P < 0.05$), whereas **p21** and **p27** mRNA expression in AC rats decreased significantly by 58% ($P < 0.03$) and 40% ($P < 0.05$) at day 7, respectively. **p21** and **p27** protein expression decreased significantly from days 3 to 21 in AC versus SH, concomitant with LV adaptive growth. Immunocytochemistry showed **p21** and **p27** expression in cardiomyocyte nuclei. Thus downregulation of **p21** and **p27** may modulate the adaptive growth of cardiomyocytes during pressure overload-induced LVH.

20/3,AB/60 (Item 60 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09585737 97446020 PMID: 9299547
Regulation of cell cycle-related genes in **rat** hepatocytes by transforming growth factor beta1.
Sugiyama A; Nagaki M; Shidoji Y; Moriwaki H; Muto Y
First Department of Internal Medicine, Gifu University School of Medicine, Gifu, 500, Japan.
Biochemical and biophysical research communications (UNITED STATES) Sep 18 **1997**, 238 (2) p539-43, ISSN 0006-291X Journal Code: 9Y8
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Transforming growth factor beta (TGF-beta) is a potent inhibitor of the proliferation of many cell types. We investigated the effects of TGF-beta1 on cyclin D1, cyclin A, **p21**, **p27**, and p53 mRNA expressions in primary cultured **rat** hepatocytes by the reverse-transcription polymerase chain reaction (RT-PCR) method. TGF-beta1 decreased the level of cyclin A mRNA in a dose-dependent manner, while it had little effect on the level of cyclin D1 mRNA. **p21** mRNA expression was greatly induced by TGF-beta1 in a p53-independent mechanism, while **p27** mRNA expression was not affected by TGF-beta1. These results suggest that TGF-beta1 may inhibit liver cell proliferation by regulating **p21** and cyclin A mRNAs. Copyright 1997 Academic Press.

20/3,AB/61 (Item 61 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09541672 97366313 PMID: 9223123
P53 synthesis and phosphorylation in the aging diet-restricted **rat** following retinoic acid administration.
Pipkin JL; Hinson WG; James SJ; Lyn-Cook LE; Duffy PH; Feuers RJ; Shaddock JG; Aly KB; Hart RW; Casciano DA
Division of Genetic Toxicology, National Center for Toxicological Research, Jefferson, AR 72079-9502, USA.

Mechanisms of ageing and development (IRELAND) Jul **1997**, 97 (1) p15-34, ISSN 0047-6374 Journal Code: LMJ
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Multiple doses of retinoic acid (RA) were administered intraperitoneally to three groups of male Fischer 344 rats over a 36 h period. The p53 isoforms from bone marrow nuclei in these three groups of rats were analyzed over time by two-dimensional polyacrylamide gel electrophoresis (PAGE) and fluorography for the incorporation of [35S]methionine (p53-synthesis) and [32P]phosphate (p53-phosphorylation). Two groups of rats, young (3.5 months) ad libitum (Y/AL) and old (28 months) ad libitum (O/AL), had free access to Purina **rat** chow; a third group of old (28 months) diet-restricted rats (O/DR) were maintained on a restricted caloric intake (60% of the AL diet) from 3 months of age. After 36 h of RA dosing, the PAGE patterns of p53 synthesis and phosphorylation in Y/AL and O/DR rats were very similar. In both groups, an increase in complexity was observed with labeling of additional isotypes possessing more acidic isoelectric values. In contrast, the O/AL animals showed a pattern of p53 isoform synthesis and phosphorylation that was considerably less complex and lacked the pronounced shift to more acidic forms following RA dosing. The p53 isoforms of O/AL rats as recognized by wild type (wt) Pab 246 antibody, were also much less dramatic in their increase to more acidic forms. Two-dimensional phospho-tryptic maps of Y/AL and O/DR rats were also very similar, both exhibiting two additional minor 32P-labeled fragments after RA dosing. The maps of O/AL rats did not show the two additional fragments following RA administration. After RA dosing, cyclin protein inhibitors (p16, **p21**, **p27**) revealed robust labeling with their respective antibodies in Y/AL and O/DR rats as analyzed by Western blotting. The O/AL animals showed marginally detectable antibody recognition of the cyclin inhibitors after RA dosing. Taken together, these data suggest that the biosynthesis and phosphorylation of p53 isoforms and the expression of cyclin dependent kinase inhibitor proteins is not significantly different between Y/AL and O/DR rats. Further, these results confirm and extend our previous observations that chronic diet-restriction attenuates the age related decline in the metabolic activity of nuclear protein products.

20/3,AB/62 (Item 62 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09509980 96194262 PMID: 8846917
CCAAT/enhancer-binding protein alpha (C/EBP alpha) inhibits cell proliferation through the **p21** (WAF-1/CIP-1/SDI-1) protein.
Timchenko NA; Wilde M; Nakanishi M; Smith JR; Darlington GJ
Department of Pathology, Baylor College of Medicine, Houston, Texas 77071, USA.
Genes & development (UNITED STATES) Apr 1 **1996**, 10 (7) p804-15, ISSN 0890-9369 Journal Code: FN3
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

C/EBPalpha has a role in growth arrest and differentiation of **mouse** preadipocytes. To study the mechanism of C/EBPalpha-induced growth arrest, we developed a cell line, HT1, that contained the human C/EBPalpha gene under Lac repressor control. IPTG-induced C/EBPalpha caused inhibition of cell proliferation and DNA synthesis as measured by colony growth assays, cell counting, and BrdU uptake. A number of proteins that are known to be involved in the regulation of the cell cycle, such as cyclin-dependent kinase (CDK)2 and CDK4, proliferating cell nuclear antigen (PCNA), p53, c-fos, and the CDK inhibitor p16 and **p27** were investigated by Western analysis. No change in their expression was observed. However, the **p21** (WAF-1/CIP-1/SDI-1) protein was significantly elevated in growth-arrested HT1 cells. Elevation of **p21**/SDI-1 mRNA (threefold)

and activation of the p[redacted]/SDI-1 promoter by C/EBPalpha did not account for the 12- to 20-f[redacted] increase in **p21**/SDI-1 protein[redacted]rotein synthesis inhibition by cycloheximide (CHX) treatment indicated that the half-life of **p21** /SDI-1 in dividing HT1 cells was approximately 30 min. However, in C/EBPalpha growth-arrested cells, the level of the **p21**/SDI-1 did not change for > 80 min after CHX addition. Our studies demonstrate that C/EBPalpha activates **p21**/SDI-1 by increasing **p21**/SDI-1 gene expression and by post-translational stabilization of **p21**/SDI-1 protein. Furthermore, induction of **p21** /SDI-1 is responsible for the ability of C/EBPalpha to inhibit proliferation because transcription of antisense **p21** /SDI-1 mRNA eliminated growth inhibition by C/EBPalpha.

20/3,AB/63 (Item 63 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09449506 98033338 PMID: 9364045
Cyclin dependent kinase inhibitors and dominant negative cyclin dependent kinase 4 and 6 promote survival of NGF-deprived sympathetic neurons.
Park DS; Levine B; Ferrari G; Greene LA
Department of Pathology and Center for Neurobiology and Behavior, Columbia University College of Physicians and Surgeons, New York, New York 10032, USA.
Journal of neuroscience (UNITED STATES) Dec 1 **1997**, 17 (23) p8975-83, ISSN 0270-6474 Journal Code: JDF
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Neuronal apoptosis plays a critical role in both normal development and disease. However, the precise molecular events controlling neuronal apoptosis are not well understood. Previously, we hypothesized that cell cycle regulatory molecules function in controlling the apoptotic pathways of trophic factor-deprived neurons. To test this hypothesis, we used the RNA alphavirus Sindbis to express three known cyclin dependent kinase inhibitors (CKIs), p16(ink4), **p21**(waf/cip), and **p27**(kip1), and dominant negative mutant forms of four known G1 cyclin dependent kinases (CDKs), Cdk2, Cdk3, Cdk4, and Cdk6, in primary cultured **rat** superior cervical ganglion sympathetic neurons. We demonstrate that expression of each of the CKIs protects the postmitotic cultured neurons from apoptotic death evoked by withdrawal of NGF. In addition, we show that expression of dominant negative forms of Cdk4 or Cdk6, but not Cdk2 or Cdk3, protects NGF-deprived sympathetic neurons from death. Such findings suggest the participation of several CDKs and their cognate cyclins in a neuronal apoptotic pathway.

20/3,AB/64 (Item 64 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09401359 97298108 PMID: 9153256
Overexpression of the integrin-linked kinase promotes anchorage-independent cell cycle progression.
Radeva G; Petrocelli T; Behrend E; Leung-Hagesteijn C; Filmus J; Slingerland J; Dedhar S
Department of Medical Biophysics, University of Toronto and Cancer Biology Research, Sunnybrook Health Science Centre, Toronto, Ontario M4N 3M5, Canada.
Journal of biological chemistry (UNITED STATES) May 23 **1997**, 272 (21) p13937-44, ISSN 0021-9258 Journal Code: HIV
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Cell adhesion to substratum has been shown to regulate cyclin A expression as well as cyclin D- and E-dependent kinases, the latter via the

up-regulation of cyclin D1 and the down-regulation of cyclin-Cdk inhibitors **p21** and **p27**, respectively. This adhesion-dependent regulation of cell cycle is thought to be mediated by integrins. Here we demonstrate that stable transfection and overexpression of the integrin-linked kinase (ILK), which interacts with the beta1 and beta3 integrin cytoplasmic domains, induces anchorage-independent cell cycle progression but not serum-independent growth of **rat** intestinal epithelial cells (IEC18). ILK overexpression results in increased expression of cyclin D1, activation of Cdk4 and cyclin E-associated kinases, and hyperphosphorylation of the retinoblastoma protein. In addition, ILK overexpression results in the expression of **p21** and **p27** Cdk inhibitors with altered electrophoretic mobilities, with the **p27** from ILK-overexpressing cells having reduced inhibitory activity. The transfer of serum-exposed IEC18 cells from adherent cultures to suspension cultures results in a rapid down-regulation of expression of cyclin D1 and cyclin A proteins as well as in retinoblastoma protein dephosphorylation. In marked contrast, transfer of ILK-overexpressing cells from adherent to suspension cultures results in continued high levels of expression of cyclin D1 and cyclin A proteins, and a substantial proportion of the retinoblastoma protein remains in a hyperphosphorylated state. These results indicate that, when overexpressed, ILK induces signaling pathways resulting in the stimulation of G1/S cyclin-Cdk activities, which are normally regulated by cell adhesion and integrin engagement.

20/3,AB/65 (Item 65 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09338755 97298090 PMID: 9153238
Protein kinase C delta inhibits the proliferation of vascular smooth muscle cells by suppressing G1 cyclin expression.
Fukumoto S; Nishizawa Y; Hosoi M; Koyama H; Yamakawa K; Ohno S; Morii H
Second Department of Internal Medicine, Osaka City University Medical School, Osaka 545, Japan.
Journal of biological chemistry (UNITED STATES) May 23 **1997**, 272 (21) p13816-22, ISSN 0021-9258 Journal Code: HIV
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
To elucidate the physiological role of protein kinase C (PKC) delta, a ubiquitously expressed isoform in vascular smooth muscle cells (VSMC), PKC delta was stably overexpressed in A7r5 cells, **rat** clonal VSMC. The [3H]thymidine incorporation in A7r5 overexpressed with PKC delta (DVs) was suppressed to 37.1 +/- 16.3% (mean +/- S.D.) of the level in control or A7r5 transfected with vector alone (EVs). The reduction of [3H]thymidine incorporation was strongly correlated with overexpressed PKC levels. Moreover, transient transfection of a dominant negative mutant of PKC delta restored the reduced proliferation in DVs. Flow cytometry analysis demonstrated that DVs were arrested in the G0/G1 phase of the cell cycle. Expression of cyclins D1 and E and retinoblastoma protein phosphorylation were reduced, while the protein levels of **p27** were elevated in DVs as compared with EVs. There were no significant differences in the expression of c-fos, c-jun, c-myc, cyclin D2, D3, cyclin-dependent kinase 2, cyclin-dependent kinase 4, and **p21** among the clones. We conclude that PKC delta inhibits the proliferation of VSMC by arresting cells in G1 via mainly inhibiting the expression of cyclin D1 and cyclin E.

20/3,AB/66 (Item 66 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09292403 97193345 PMID: 9040936
Cyclin-dependent kinase inhibitor expression in pulmonary Clara cells transformed with SV40 large T antigen in transgenic mice.
Magdaleno SM; Wang G; Mireles VL; Ray MK; Finegold MJ; DeMayo FJ

Department of Cell Biology, Baylor College of Medicine, Houston, Texas 77030, USA.
Cell growth & differentiation (UNITED STATES) Feb **1997**, 8 (2) p145-55, ISSN 1044-9523 Journal Code: AYH
Contract/Grant No.: HL 47620, HL, NHLBI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Expression of cell cycle regulatory genes in **mouse** lung was investigated in transgenic models for Clara cell transformation. Clara cells were transformed by generating transgenic mice in which the SV40 large T antigen was expressed under the control of the **mouse** Clara cell M(r) 10,000 protein promoter. The resulting lung tumors express the large T antigen in normal Clara cells and in tumors, and these tumors express reduced levels of CC10 mRNA. The expression of cell cycle regulatory protein, p53, and the cyclin-dependent kinase inhibitors was analyzed by Northern blot analysis and in situ hybridization throughout the progression of Clara cell transformation in the lung. Increases in specific cyclin-dependent kinase inhibitor steady-state mRNA levels were detected in p15, p18, **p27** , and p57 during tumor progression. The expression of p15, p57, and **p21** mRNAs were verified by in situ hybridization. Using this approach, regulatory genes have been identified that may be involved in the regulation of Clara cell differentiation.

20/3,AB/67 (Item 67 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09220369 96413751 PMID: 8816905
Differential regulation of **p27** and cyclin D1 by TGF-beta and EGF in C3H 10T1/2 **mouse** fibroblasts.
Ravitz MJ; Yan S; Dolce C; Kinniburgh AJ; Wenner CE
Department of Biochemistry, Roswell Park Cancer Institute, Buffalo, New York 14263, USA.
Journal of cellular physiology (UNITED STATES) Sep **1996**, 168 (3) p510-20, ISSN 0021-9541 Journal Code: HNB
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Previously, we found that stimulation of C3H 10T1/2 **mouse** fibroblasts with TGF-beta leads to the striking and rapid down-regulation of p27kip1 expression during G1 phase. Here, we demonstrate that TGF-beta treatment of C3H 10T1/2 cells does not alter the steady-state level of Kip1 message sufficiently to account for the observed down-regulation of **p27** . This demonstrates that TGF-beta-induced down regulation of p27kip1 occurs at a post-transcriptional level, consistent with a degradative mechanism of p27kip1 down-regulation. Epidermal growth factor (EGF) does not lead to the rapid down-regulation of **p27** observed following treatment of cells with TGF-beta. Also in contrast with TGF-beta, EGF causes a strong upregulation of cyclin D1, while neither growth factor affects cdk4 protein levels. These results imply that in this cell type TGF-beta overcomes an inhibitory threshold to cdk activation by cyclin-dependent kinase inhibitors primarily through down-regulation of **p27** , while EGF overcomes this threshold predominantly through upregulation of cyclin D1 levels. This divergence in pathways may explain why TGF-beta-induced cell cycle kinetics are slower than those of EGF in these cells, and the ability of TGF-beta to delay EGF-induced cell cycle kinetics to its own, slower kinetics. In support of this hypothesis, TGF-beta prevents EGF-induced upregulation of cyclin D1 levels, while TGF-beta is still able to induce **p27** down-regulation even in the presence of EGF. In contrast to the case with **p27** degredation, neither TGF-beta nor EGF have an observable effect on the steady-state levels of **p21** in this cell type.

20/3,AB/68 (Item 68 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09187508 96343851 PMID: 8760794
Induction of cell cycle regulatory proteins in anti-immunoglobulin-stimulated mature B lymphocytes.
Solvason N; Wu WW; Kabra N; Wu X; Lees E; Howard MC
Department of Immunology, DNAX Research Institute, Palo Alto, California 94304-1104, USA.
Journal of experimental medicine (UNITED STATES) Aug 1 **1996**, 184 (2) p407-17, ISSN 0022-1007 Journal Code: I2V
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Progression through the cell cycle is a tightly controlled process that integrates signals generated at the plasma membrane with the proteins that form the cell cycle machinery. The current study chronicles the induction of cyclins, cyclin-dependent kinases (cdk), and cdk inhibitors in low density primary **mouse** B lymphocytes after anti-immunoglobulin plus interleukin 4 (IgM + IL-4) stimulation. In this system, > 85% of cells remain in the G0/G1 phase of cell cycle for an initial 24-h period, followed by entry of up to 50% of the cells into S phase, commencing around 30 h and peaking at 48 h. Extensive time course analyses of these anti-IgM + IL-4-stimulated B cells revealed that the G1-associated D-type cyclins D2 and D3 were induced by 3 h after stimulation, and that cyclins E, A, and B were subsequently induced sequentially, beginning at mid-G1, G1/S transition, and S phase, respectively. The G1-associated cyclin D1 was not expressed at any stage of the anti-Ig + IL-4-induced B cell cycle. cdk2, cdk4, and cdk6 were induced during G1, whereas cell division cycle-2 (cdc2) was induced concomitantly with S phase. Irrespective of their expression, the kinases cdk2 and cdc2 were only active from S phase onwards, suggesting that productive cyclin/kinase complex formation did not occur until that time. Cell cycle inhibitors **p21** and p19 were induced by anti-Ig + IL-4, peaking in expression at mid-G1 and S phase, respectively. Stimulation of low density B cells with anti-Ig + IL-4 caused rapid down regulation of the **p27** inhibitor, however this protein was reexpressed at 54-96 h after stimulation. In contrast, B cells stimulated with anti-CD40, a stimulus which induces long-term B cell proliferation, permanently down regulated **p27**. These findings are consistent with the concept that **p27** reexpression contributes to the G1 arrest that follows antigen receptor crosslinking. Low density B cells cultured in the viability-enhancing cytokine IL-4 alone also showed induction of D2 and D3 cyclin expression. However, the D2 expression was transient, and the D3 expression was substantially lower than that observed in B cells induced to proliferate by anti-Ig + IL-4. This partial induction of D2 and D3 expression may explain IL-4's ability to promote B cell entry into G1 but not S phase of cell cycle, and furthermore, its ability to truncate G1 progression when B cells are subsequently stimulated with anti-Ig.

20/3,AB/69 (Item 69 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09174665 97073312 PMID: 8916036
Temporal patterns of gene expression of G1-S cyclins and cdks during the first and second mitotic cell cycles in **mouse** embryos.
Moore GD; Ayabe T; Kopf GS; Schultz RM
Department of Obstetrics and Gynecology, University of Pennsylvania, Philadelphia 19104-6018, USA.
Molecular reproduction and development (UNITED STATES) Nov **1996**, 45 (3) p264-75, ISSN 1040-452X Journal Code: AN7
Contract/Grant No.: HD22732, HD, NICHD
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Cell-cycle progression in somatic cells is regulated by a family of cyclins and cyclindependen[redacted]inases (cdks) that form specif[redacted]complexes as a function of cell-cycle progression. However, the transcript abundance of G1-S cyclins and cdks during the meiotic and mitotic cell cycles of mammalian embryos has not been previously reported. Using a reverse transcription-polymerase chain reaction (PCR) assay that detects changes in either mRNA abundance or polyadenylation state, we examined the relative levels of gene expression for the G1-S cyclins and cdks, as well as for **p21**, **p27**, and the retinoblastoma (Rb) gene in **mouse** oocytes, metaphase II-arrested eggs, and 1-2-cell embryos. The PCR products for cyclins D1, D3, and A, as well as cdk4, **p21**, and Rb, displayed similar levels in meiotically incompetent and competent oocytes, as well as in metaphase II-arrested eggs. The levels of PCR products for cyclin D2, **p27**, and two forms of cdk2 were similar in meiotically incompetent and competent oocytes but decreased during oocyte maturation. Finally, the level of PCR products for cyclin E and cdk2 gradually decreased during the progression from meiotically incompetent oocytes to metaphase II-arrested eggs. When the levels of PCR products for the G1-S regulatory genes were evaluated during the first and second mitotic cell cycles, four main patterns were found: 1) steady levels for cyclin A; 2) steady levels followed by a 2-3-fold increase during the G2 phase of the second mitotic cell cycle for cyclins D1, E, cdk2, and **p21**; 3) a transient increase during the S and/or G2 phases of the first mitotic cell cycle for **p27**, cyclin D3, and the two forms of cdk2; and 4) higher levels during the first cell cycle and then a decrease with lower levels during the second mitotic cell cycle for cyclin D2 and Rb. cdk4 expression displayed a combination of patterns 2 and 3. The increase in the amount of PCR product for the cdk4 gene during the first mitotic cell cycle was due to polyadenylation, whereas the increase in the amount of PCR product for cdk4, cdk2, and cyclins D1 and E in the second mitotic cell cycle was a product of activation of the embryonic genome.

20/3,AB/70 (Item 70 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09157412 97197640 PMID: 9045936
Expression of **p21** (waf-1/cip-1) is significantly induced in the livers of LEC rats with chronic liver injury.
Sawada N; Kojima T; Obata H; Isomura H; Atsumi S; Sawaki M; Tsuzuki N; Tobioka H; Kokai Y; Satoh M; Mori M
Department of Pathology, Cancer Research Institute, Sapporo Medical University School of Medicine, Chuo-ku.
Japanese journal of cancer research (JAPAN) Nov **1996**, 87 (11) p1102-5, ISSN 0910-5050 Journal Code: HBA
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
It is reported that hepatocytes isolated from LEC rats with chronic liver injury show reduced growth activity in primary culture. To elucidate the molecular basis of this phenomenon, we examined expression of **p21** (waf-1/ciP-1) and **p27**, cyclin-dependent kinase inhibitors, by northern blot analysis. The expression of **p21**(waf-1/cip-1) in the LEC **rat** liver was 3-fold higher than that of age-matched SD **rat** liver, while there was no significant difference in **p27** expression level. Western blot analysis also revealed a significant increase in **p21**(waf-1/cip-1) in the nuclear matrix fraction of the LEC **rat** liver. Immunohistochemically, **p21**(waf-1/cip-1) was detected in the nuclei of normal LEC **rat** hepatocytes, but not in those of hepatocellular carcinoma cells, suggesting selective growth of neoplastic hepatocytes.

20/3,AB/71 (Item 71 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09136187 97053985 PMID: 8898364

Induction of p18INK4c and its predominant association with CDK4 and CDK6 during myogenic differentiation.

Franklin DS; Xiong Y

Lineberger Comprehensive Cancer Center, Chapel Hill, North Carolina 27599, USA.

Molecular biology of the cell (UNITED STATES) Oct **1996**, 7 (10) p1587-99, ISSN 1059-1524 Journal Code: BAU

Contract/Grant No.: CA-65572, CA, NCI

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Terminal cell differentiation involves permanent withdrawal from the cell division cycle. The inhibitors of cyclin-dependent kinases (CDKs) are potential molecules functioning to couple cell cycle arrest and cell differentiation. In murine C2C12 myoblast cells, G1 CDK enzymes (CDK2, CDK4, and CDK6) associate with four CDK inhibitors: p18INK4c, p19INK4d, **p21**, and p27Kip1. During induced myogenesis, **p21** and its associated CDK proteins underwent an initial increase followed by a decrease as cells became terminally differentiated. The level of **p27** protein gradually increased, but the amount of total associated CDK proteins remained unchanged. p19 protein decreased gradually during differentiation, as did its associated CDK4 protein. In contrast, p18 protein increased 50-fold, from negligible levels in proliferating myoblasts to clearly detectable levels within 8-12 h of myogenic induction. This initial rise was followed by a precipitous increase between 12 and 24 h postinduction, with p18 protein finally accumulating to its highest level in terminally differentiated cells. Induction of p18 correlated with increased and sequential complex formation--first increasing association with CDK6 and then with CDK4 over the course of myogenic differentiation. All of the CDK6 and half of the CDK4 were complexed with p18 in terminally differentiated C2C12 cells as well as in adult **mouse** muscle tissue. Finally, kinase activity of CDK2 and CDK4 decreases as C2C12 cells differentiate, whereas the CDK6 kinase activity is low in both proliferating myoblasts and differentiated myotubes. Our results indicate that p18 may play a critical role in causing and/or maintaining permanent cell cycle arrest associated with mature muscle formation.

20/3,AB/72 (Item 72 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08805140 96079266 PMID: 8534916

Redistribution of the CDK inhibitor **p27** between different cyclin.CDK complexes in the **mouse** fibroblast cell cycle and in cells arrested with lovastatin or ultraviolet irradiation.

Poon RY; Toyoshima H; Hunter T

Molecular Biology and Virology Laboratory, Salk Institute for Biological Studies, La Jolla, California 92037-1099, USA.

Molecular biology of the cell (UNITED STATES) Sep **1995**, 6 (9) p1197-213, ISSN 1059-1524 Journal Code: BAU

Contract/Grant No.: CA-14195, CA, NCI; CA-39780, CA, NCI

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The cyclin-dependent kinase (CDK) inhibitor **p27** binds and inhibits the kinase activity of several CDKs. Here we report an analysis of the behavior and partners of **p27** in Swiss 3T3 **mouse** fibroblasts during normal mitotic cell cycle progression, as well as in cells arrested at different stages in the cycle by growth factor deprivation, lovastatin treatment, or ultraviolet (UV) irradiation. We found that the level of **p27** is elevated in cells arrested in G0 by growth factor deprivation or contact inhibition. In G0, **p27** was predominantly monomeric, although some portion was associated with residual cyclin A.Cdk2. During

G1, all of **p27** was associated with cyclin D1.Cdk4 and was then redistributed to cyclin [redacted]dk2 as cells entered S phase. [redacted] loss of the monomeric **p27** pool as cyclins accumulate in G1 is consistent with the in vivo and in vitro data showing that **p27** binds better to cyclin.CDK complexes than to monomeric CDKs. In growing cells, the majority of **p27** was associated with cyclin D1 and the level of **p27** was significantly lower than the level of cyclin D1. In cells arrested in G1 with lovastatin, cyclin D1 was degraded and **p27** was redistributed to cyclin A.Cdk2. In contrast to **p21** (which is a **p27**-related CDK inhibitor and is induced by UV irradiation), the level of **p27** was reduced after UV irradiation, but because cyclin D1 was degraded more rapidly than **p27**, there was a transient increase in binding of **p27** to cyclin A.Cdk2. These data suggest that cyclin D1.Cdk4 acts as a reservoir for **p27**, and **p27** is redistributed from cyclin D1.Cdk4 to cyclin A.Cdk2 complexes during S phase, or when cells are arrested by growth factor deprivation, lovastatin treatment, or UV irradiation. It is likely that a similar principle of redistribution of **p27** is used by the cell in other instances of cell cycle arrest.

20/3,AB/73 (Item 73 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08412919 94306519 PMID: 8033213
p27, a novel inhibitor of G1 cyclin-Cdk protein kinase activity, is related to **p21**.
Toyoshima H; Hunter T
Molecular Biology and Virology Laboratory, Salk Institute, La Jolla, California 92037.
Cell (UNITED STATES) Jul 15 **1994**, 78 (1) p67-74, ISSN 0092-8674 Journal Code: CQ4
Contract/Grant No.: CA14195, CA, NCI; CA39780, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Using a yeast interaction screen to search for proteins that interact with cyclin D1-Cdk4, we identified a 27 kDa **mouse** protein related to the **p21** cyclin-Cdk inhibitor. **p27** interacts strongly with D-type cyclins and Cdk4 in vitro and more weakly with cyclin E and Cdk2. In **mouse** fibroblasts, **p27** is associated predominantly with cyclin D1-Cdk4. Recombinant **p27** is a potent inhibitor of cyclin D1-Cdk4 and cyclin A-Cdk2 protein kinase activity and a weaker inhibitor of cyclin B1-Cdc2. Overexpression of **p27** in Saos-2 cells causes G1 arrest. **p27** protein levels do not change as serum-stimulated quiescent **mouse** fibroblasts progress through the cell cycle. **p27** is identical to p27Kip1, a cyclin-Cdk inhibitor present in TGF beta-treated cells. **p27** has the hallmarks of a negative regulator of G1 progression and may mediate TGF beta-induced G1 arrest.

20/3,AB/74 (Item 74 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04720437 81072427 PMID: 6255175
Analysis of secondary modifications of **mouse** mammary tumor virus proteins by two-dimensional gel electrophoresis.
Nusse R; Janssen H; de Vries L; Michalides R
Journal of virology (UNITED STATES) Aug **1980**, 35 (2) p340-8, ISSN 0022-538X Journal Code: KCV
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The structural proteins of **mouse** mammary tumor virus (MMTV) were analyzed by two-dimensional electrophoresis on isoelectric focusing and sodium dodecyl sulfate gels. Many of the viral proteins displayed

heterogeneity in charge due to variable contents of carbohydrates (in particular, sialic acid) and phosphate residues. Neuraminidase treatment of the virions influenced the isoelectric pattern of the envelope glycoproteins. The glycoproteins of an MMTV variant which was attenuated by replication in feline kidney cells had different isoelectric points. This suggested that the acquisition of an altered carbohydrate configuration had changed the host range of the virus. The major MMTV structural core protein, **p27**, consisted of two species, which had identical iodinated tryptic peptide compositions but differed in phosphate contents. Another MMTV phosphoprotein, **p21** , was separated into four different phosphorylated species. Phosphorylation of **p21** could be performed in vitro by the MMTV virion-associated protein kinase. This enzyme also has a high affinity for MMTV p30 as a substrate. Possible functions of this enzyme are discussed.

20/3,AB/75 (Item 75 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04326413 81218423 PMID: 7195432
Rat sarcoma virus: further analysis of individual viral isolates and the gene product.
Young HA; Rasheed S; Sowder R; Benton CV; Henderson LE
Journal of virology (UNITED STATES) Apr **1981**, 38 (1) p286-93,
ISSN 0022-538X Journal Code: KCV
Contract/Grant No.: CA-27246-01, CA, NCI; N01-C0-75380, PHS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Rasheed **rat** sarcoma virus, derived by in vitro cocultivation of two **rat** cell lines (Rasheed et al., Proc. Natl. Acad. Sci. U.S.A. 75:2972-2976, 1978), has been reported to code for a protein of 29,000 Mr, immunologically related to the 21,000 Mr src gene product of Harvey and Kirsten sarcoma viruses. **Rat** sarcoma virus p29 was thought to contain at least part of a **rat** type C virus structural protein, since antiserum prepared against whole **rat** virus was able to immunoprecipitate **rat** sarcoma virus p29 but not Harvey or Kirsten sarcoma virus **p21** (Young et al., Proc. Natl. Acad. Sci. U.S.A. 76:3523-3527, 1979). We now report that antiserum directed against **rat** type C virus p15, but not viral p12, p10, or **p27**, immunoprecipitated **rat** sarcoma virus p29. The p15 antiserum was also able to immunoprecipitate both denatured p29 and a peptide derived by V-8 protease cleavage of p29, indicating that this antiserum contains antibodies directed against primary amino acid determinants. Finally, five separate isolates of **rat** sarcoma virus were found to code for p29, which indicates that a highly specific site of recombination is involved in the generation of sarcoma viruses in **rat** cells.

20/3,AB/76 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13104756 BIOSIS NO.: 200100311905
Modulation of myeloid progenitor cell proliferation by cyclin-dependent kinase inhibitors as determined in p18INK4C, p21cip1/waf1, p27kip1 and dual p18/**p21** and p18/**p27** gene knock-out mice.
AUTHOR: Broxmeyer H E(a); Cooper S(a); Hangoc G(a); Mantel C(a); Franklin D S
AUTHOR ADDRESS: (a)Dept. Microbiology/Immunology, Walther Oncology Center, Indiana University School of Medicine and Walther Cancer Institute, Indianapolis, IN**USA
JOURNAL: Blood 96 (11 Part 1):p539a November 16, **2000**
MEDIUM: print
CONFERENCE/MEETING: 42nd Annual Meeting of the American Society of

Hematology San Francisco, California, USA December 01-05, 2000
SPONSOR: American Society of Hematology
ISSN: 0006-4971
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Cyclin-dependent kinase inhibitors are involved in cell-cycle regulation. Use of gene knock-out (-/-) mice has suggested a positive role for p21cip1 (Blood 88:3710, 1996) and a negative role for p27kip1 (Cell 85:733, 1996) in proliferation of myeloid progenitor cells (MPC). Recently, p18INK4C -/-, dual p18/**p27** -/- (Gene Develop 12:2899, 1998) and p18/**p21** -/- (MCB 20:6147, 2000) mice have been produced allowing evaluation of myelopiesis in these genotypes compared with single null controls. Marrow and spleen cells were assessed for absolute numbers and cycling status of MPC. Marrow CFU-GM were assessed for responsiveness to synergistic stimulation with GM-CSF plus steel factor (SLF). Absolute numbers of CFU-GM, BFU-E, and CFU-GEMM were decreased 60-75% in marrow and 39- 85% in spleens of **p21** -/- mice and increased by 82-242% in marrow and 1106-1300% in spleens of **p27** -/- mice compared to controls. In control mice, the percent MPC in S-phase was 35-39% in marrow and 0-2% in spleen. Compared to controls, cycling of MPC from **p21** -/- mice was decreased 99% in marrow and unchanged in spleen. Cycling of MPC from **p27** -/- mice was increased 71-150% in marrow and 51-71% in spleens. The MPC profile of p18 -/- mice was similar to that of **p21** -/- mice. MPC characteristics of p18/**p21** -/- mice were similar to **p21** -/- and p18 -/- mice. However, synergistic stimulation by GM-CSF plus SLF on colony formation was decreased/absent on **p21** -/-, but apparent with p18 -/- cells. The p18 -/- effect dominated in the p18/**p21** -/- cells where synergism was detected. In p18/**p27** -/- mice, MPC characteristics of the p18 -/- mice dominated that of the **p27** -/- mice. Numbers and cycling of marrow MPC were decreased compared to control mice. Numbers of MPC in spleens of p18/**p27** -/- mice were significantly below that of **p27** -/- mice. Moreover, MPC of p18/**p27** -/- mice were in a slow cycling state, which contrasted with the rapid cycling **p27** -/- MPC. In contrast, synergism was not detected with **p27** -/- MPC and this lack of synergism dominated with p18/**p27** -/- cells. Overall, the results suggest that there is decreased MPC proliferation in p18 -/- mice suggesting a positive role for p18 similar to that of **p21**, and that the positive effects of p18 dominate over the negative effects of **p27** in MPC proliferation. However, the cyclin-dependent kinase inhibitors appear to differentially regulate responses of CFU-GM to synergistic cell proliferation. This underscores the complexity of cell cycle regulators and that loss of one can sometimes be compensated by loss of another.

2000

13104508 BIOSIS NO.: 200100311657
GATA-2 down-regulates c-myc and affects cytokine-dependent growth of hematopoietic cells.
AUTHOR: Ezoe Sachiko(a); Matsumura Itaru(a); Tanaka Hirokazu(a); Kawasaki Akira(a); Machii Takashi(a); Enver Tariq(a); Kanakura Yuzuru(a)
AUTHOR ADDRESS: (a)Hematology and Oncology, Osaka University Graduate School of Medicine, Suita, Osaka**Japan
JOURNAL: Blood 96 (11 Part 1):p285a November 16, **2000**
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CONFERENCE/MEETING: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000

SPONSOR: American Society of Hematology
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LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: GATA-2 plays essential roles in the development of hematopoietic cells. GATA-2 knock out mice were embryonic lethal due to the lack of definitive hematopoiesis. However, GATA-2 was also reported to inhibit the growth of normal hematopoietic progenitor cells. To examine the effects of GATA-2 on the growth of hematopoietic cells, we here utilized GATA-2/ER consisting of full-length GATA-2 and ligand-binding domain of estrogen receptor, in which GATA-2 activities are induced by estradiol. We expressed GATA-2/ER in IL-3-dependent cell lines Ba/F3, FDCP-1 and 32D. The estradiol-induced GATA-2 inhibited the IL-3-dependent growth of Ba/F3, FDCP-1 and 32D almost completely, but apparent cell death was not induced in these cultures. Next, we introduced c-mpl (TPO receptor), c-kit (SCF receptor) and G-CSFR/gp130 (a chimeric receptor composed of the extracellular domain of G-CSFR and the intracellular domain of gp130) into GATA-2/ER-transfected Ba/F3. In the absence of estradiol, TPO, SCF and G-CSF promoted the growth of the corresponding clones expressing their receptors, respectively. During the culture with TPO, GATA-2 caused severe growth inhibition but not cell death. By contrast, GATA-2 provoked severe growth suppression and apoptosis in c-kit transfected Ba/F3 under the culture with SCF and in G-CSFR/gp130-transfected Ba/F3 under the culture with G-CSF. Next, we examined the expression of growth regulatory molecules during GATA-2-induced growth suppression of Ba/F3 under the culture with IL-3. We did not detect significant changes in the expression of growth inhibitory molecules such as CDK inhibitors (p16, p15, p18, p19, **p21**, **p27**, p57), p53 and p19ARF by Northern blot analysis. Among growth promoting molecules, furthermore, we could not detect apparent changes in expression of cyclin D1, D2, D3, cdk6, or cdc2. In contrast, c-myc expression was found to decrease after the 4-h estradiol treatment, and cdk4 expression decreased at 8 h, followed by the decline of cdk2, cyclin A, and cyclin B expression from 72 to 120 h. To examine the significance of GATA-2-mediated repression of c-myc cdk4, we introduced c-myc and cdk4 into GATA-2/ER-transfected Ba/F3. As a result, overexpression of c-myc canceled GATA-2-induced growth suppression by about 70%, and that of cdk4 by about 30%. These results suggested that GATA-2 might suppress the growth of hematopoietic cells through the down-regulation of c-myc and partly through that of cdk4.

2000

20/3,AB/78 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12920900 BIOSIS NO.: 200100128049
Osteoclast differentiation is associated with transient upregulation of cyclin-dependent kinase inhibitors p21WAF1/CIP1 and p27KIP1.
AUTHOR: Okahashi Nobuo; Murase Yoshiyuki; Koseki Takeyoshi; Sato Tsuyoshi; Yamato Kenji; Nishihara Tatsuji(a)
AUTHOR ADDRESS: (a)Department of Oral Microbiology, Kyushu Dental College, 2-6-1, Manazuru, Kokurakita ku, Kita-Kyushu, 803-8580: tatsujin@kyu-dent.ac.jp**Japan
JOURNAL: Journal of Cellular Biochemistry 80 (3):p339-345 27 November-21 December, **2000**
MEDIUM: print
ISSN: 0730-2312
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Osteoclasts, bone resorbing multinucleated cells, develop from monocyte-macrophage lineage cells in the presence of osteoclast differentiation factor (ODF, also called RANKL/TRANCE/OPGL) and macrophage colony-stimulating factor (M-CSF). M-CSF-dependent bone marrow macrophages (M-BMMPHIs) from **mouse** bone marrow cells have been shown to differentiate into osteoclast-like multinucleated cells (OCLs) in the presence of soluble ODF/RANKL (sODF/RANKL) and M-CSF within 3 days. In this study, we found that stimulation of M-BMMPHIs with sODF/RANKL induced a transient expression of cyclin-dependent kinase inhibitors (CDK inhibitors) p21WAF1/CIP1 and p27KIP1 by 24 h. The CDK inhibitor proteins disappeared by 48 h. Tumor necrosis factor alpha (TNF-alpha), which is reported to stimulate OCL differentiation, stimulated p21WAF1/CIP1 and p27KIP1 expression in M-BMMPHIs as well. However, M-CSF alone did not stimulate the expression of the two CDK inhibitors. To clarify the role of p21WAF1/CIP1 and p27KIP1 in osteoclastogenesis, accumulation of these CDK inhibitors was aborted by antisense oligonucleotides. Treatment with p21WAF1/CIP1 antisense oligonucleotide alone, or p27KIP1 antisense oligonucleotide alone, showed a limited inhibitory effect on OCL formation. However, treatment with a mixture of these two antisense oligonucleotides strongly inhibited OCL formation. These results suggest that a combined modulation of the CDK inhibitors p21WAF1/CIP1 and p27KIP1 may be involved in osteoclast differentiation induced by ODF/RANKL.

2000

20/3,AB/79 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12918637 BIOSIS NO.: 200100125786
Expression and regulation of cyclin-dependent kinase inhibitors **p21** & **p27** in rheumatoid arthritis.
AUTHOR: Zahra D G(a); Wu Y R(a); Handel M L(a)
AUTHOR ADDRESS: (a)Arthritis and Inflammation Research Program, Garvan Institute of Medical Research, Sydney**Australia
JOURNAL: Cell Biology International 24 (12):p931 **2000**
MEDIUM: print
CONFERENCE/MEETING: 7th International Congress of Cell Biology Gold Coast, Queensland, Australia September 24-28, 2000
ISSN: 1065-6995
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

20/3,AB/80 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12916964 BIOSIS NO.: 200100124113
p21(CIP1) and **p27**(Kip1) mediate perinatal cell cycle exit in **mouse** myocardium.
AUTHOR: Zhan Song(a); Schneider Michael D(a)
AUTHOR ADDRESS: (a)Baylor Coll of Medicine, Houston, TX**USA
JOURNAL: Circulation 102 (18 Supplement):pII139 October 31, **2000**
MEDIUM: print
CONFERENCE/MEETING: Abstracts from Scientific Sessions 2000 New Orleans, Louisiana, USA November 12-15, 2000
ISSN: 0009-7322
RECORD TYPE: Citation
LANGUAGE: English

SUMMARY LANGUAGE: English
2000

20/3,AB/81 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12893390 BIOSIS NO.: 200100100539
Regulation of vascular cell growth by cell cycle proteins.
AUTHOR: Nabel E G(a)
AUTHOR ADDRESS: (a)National Heart, Lung, and Blood Institute, NIH, Bethesda, MD**USA
JOURNAL: Journal of Submicroscopic Cytology and Pathology 32 (3):p481 July, **2000**
MEDIUM: print
CONFERENCE/MEETING: XIth International Vascular Biology Meeting Geneva, Switzerland September 05-09, 2000
ISSN: 1122-9497
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

20/3,AB/82 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12827894 BIOSIS NO.: 200100035043
Stem cell repopulation efficiency but not pool size is governed by p27kip1.
AUTHOR: Cheng Tao(a); Rodrigues Neil; Dombkowski David; Stier Sebastian; Scadden David T(a)
AUTHOR ADDRESS: (a)Massachusetts General Hospital AIDS Research Center and MGH Cancer Center, Harvard Medical School, 149 13th Street, Room 5212, Boston, MA, 02129: cheng-tao@mgh.harvard.edu, scadden.david@mgh.harvard.edu**USA
JOURNAL: Nature Medicine 6 (11):p1235-1240 November, **2000**
MEDIUM: print
ISSN: 1078-8956
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Sustained blood cell production requires preservation of a quiescent, multipotential stem cell pool that intermittently gives rise to progenitors with robust proliferative potential. The ability of cells to shift from a highly constrained to a vigorously active proliferative state is critical for maintaining stem cells while providing the responsiveness necessary for host defense. The cyclin-dependent kinase inhibitor (CDKI), p21cip1/waf1 (**p21**) dominates stem cell kinetics. Here we report that another CDKI, p27kip1 (**p27**), does not affect stem cell number, cell cycling, or self-renewal, but markedly alters progenitor proliferation and pool size. Therefore, distinct CDKIs govern the highly divergent stem and progenitor cell populations. When competitively transplanted, **p27**-deficient stem cells generate progenitors that eventually dominate blood cell production. Modulating **p27** expression in a small number of stem cells may translate into effects on the majority of mature cells, thereby providing a strategy for potentiating the impact of transduced cells in stem cell gene therapy.

2000

20/3,AB/83 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12772567 BIOSIS NO.: 200000526190
In vivo expression of human papillomavirus oncoproteins in alters cell cylce regulatory protein expression.
AUTHOR: Crish James F(a); Bone Frederic(a); Balasubramanian Sivaprakasam(a); Zaim Tarif M(a); Wagner Thomas(a); Yun Jeung(a); Rorke Ellen A(a); Eckert Richard L(a)
AUTHOR ADDRESS: (a)Departments of Physiology and Biophysics, and Environmental Health Sciences, Case Western Reserve University School of Medicine, 2109 Adelbert Road, Cleveland, OH, 44106-4970**USA
JOURNAL: International Journal of Molecular Medicine 6 (Supplement 1):pS18 **2000**
MEDIUM: print
CONFERENCE/MEETING: Joint Meeting of the 5th World Congress on Advances in Oncology and the 3rd International Symposium on Molecular Medicine Crete, Greece October 19-21, 2000
ISSN: 1107-3756
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

20/3,AB/84 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12769481 BIOSIS NO.: 200000523104
Cell cycle exit during terminal erythroid differentiation is associated with accumulation of p27Kip1 and inactivation of cdk2 kinase.
AUTHOR: Hsieh Fen F; Barnett Lou Ann; Green Wayne F; Freedman Karen; Matushansky Igor; Skoultchi Arthur I; Kelley Linda L(a)
AUTHOR ADDRESS: (a)Department of Medicine, University of Utah School of Medicine, 50 North Medical Dr, AR159, Salt Lake City, UT, 84132**USA
JOURNAL: Blood 96 (8):p2746-2754 October 15, **2000**
MEDIUM: print
ISSN: 0006-4971
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Progression through the mammalian cell cycle is regulated by cyclins, cyclin- dependent kinases (CDKs), and cyclin-dependent kinase inhibitors (CKIs). The function of these proteins in the irreversible growth arrest associated with terminally differentiated cells is largely unknown. The function of Cip/Kip proteins p21Cip1 and p27Kip1 during erythropoietin-induced terminal differentiation of primary erythroblasts isolated from the spleens of mice infected with the anemia-inducing strain of Friend virus was investigated. Both p21Cip1 and p27Kip1 proteins were induced during erythroid differentiation, but only p27Kip1 associated with the principal G1 CDKs-cdk4, cdk6, and cdk2. The kinetics of binding of p27Kip1 to CDK complexes was distinct in that p27Kip1 associated primarily with cdk4 (and, to a lesser extent, cdk6) early in differentiation, followed by subsequent association with cdk2. Binding of p27Kip1 to cdk4 had no apparent inhibitory effect on cdk4 kinase activity, whereas inhibition of cdk2 kinase activity was associated with p27Kip1 binding, accumulation of hypo-phosphorylated retinoblastoma protein, and G1 growth arrest. Inhibition of cdk4 kinase activity late in differentiation resulted from events other than p27Kip1 binding or loss of cyclin D from the complex. The data demonstrate that p27Kip1 differentially regulates the activity of cdk4 and cdk2 during terminal

erythroid differentiation and suggests a switching mechanism whereby cdk4 functions to sequester p2[redacted]p1 until a specified time in d[redacted]erentiation when cdk2 kinase activity is targeted by p27Kip1 to elicit G1 growth arrest. Further, the data imply that p21Cip1 may have a function independent of growth arrest during erythroid differentiation.

2000

20/3,AB/85 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12759364 BIOSIS NO.: 200000512987
A vitamin D3 analog induces a G1-phase arrest in CaCo-2 cells by inhibiting cdk2 and cdk6: Roles of cyclin E, p21Waf1, and p27Kip1.
AUTHOR: Scaglione-Sewell B A; Bissonnette M; Skarosi S; Abraham C; Brasitus T A(a)
AUTHOR ADDRESS: (a)Gastroenterology Section, Department of Medicine, University of Chicago, 5841 South Maryland Avenue, Chicago, IL, 60637** USA
JOURNAL: Endocrinology 141 (11):p3931-3939 November, **2000**
MEDIUM: print
ISSN: 0013-7227
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Previous studies by our laboratory have shown that a noncalcemic fluorinated analog of 1alpha,25-dihydroxyvitamin D3, 1alpha,25-dihydroxy-16-ene-23-yne-26,27-hexafluorocholcalciferol (F6-D3), significantly reduced the frequency of colonic adenomas and completely abolished the development of colonic adenocarcinomas in rats treated with azoxymethane. The mechanisms involved in this analog's chemopreventive actions, however, remain unclear. In the present study, we now show that although both 1alpha,25-dihydroxyvitamin D3 and F6-D3 inhibited the proliferation of CaCo-2 cells, a human colonic adenocarcinoma cell line, by increasing their doubling times, only F6-D3 caused an arrest of these cells in the G1 phase of their cell cycle. This arrest was accompanied by an increase in the expression of the cyclin-dependent kinase (cdk) inhibitor proteins, p21Waf1 and p27Kip1, which served to decrease the activity of cyclin-dependent kinase 2 and cyclin-dependent kinase 6, whereas the expression and phosphorylation of pRB were unchanged. In contrast to the increased expression of these cdk inhibitors, the expression of cyclin E was decreased, which further inhibited the activity of cyclin-dependent kinase 2. Collectively, the inhibition of these cyclin-dependent kinases served to arrest the CaCo-2 cells, independent of changes in pRB. Furthermore, antibody neutralization studies suggest that transforming growth factor-beta may mediate the coassociations between cdk2 and p27Kip1 and cyclin E induced by F6-D3. These data indicate that cell cycle arrest may, at least in part, underlie the chemopreventive actions of F6-D3 observed in the azoxymethane model of colon cancer. Furthermore, if the antiproliferative action observed in CaCo-2 cells also occurs in human colonic epithelium, F6-D3 may have chemopreventive potential against human colon cancer, as well.

2000

20/3,AB/86 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12733795 BIOSIS NO.: 200000187297
eNOS inhibition of prolifer[redacted]on: A role for p21Sdi1/Cip1/Wa[redacted]and p27kip1.
AUTHOR: Holt Cathy M(a)
AUTHOR ADDRESS: (a)Cardiovascular Research Group, Clinical Sciences Centre, Northern General Hospital, Sheffield, S5 7AU**UK
JOURNAL: Cardiovascular Research 47 (4):p640-641 September, **2000**
MEDIUM: print
ISSN: 0008-6363
DOCUMENT TYPE: Editorial
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

20/3,AB/87 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12722840 BIOSIS NO.: 200000476342
A comparison of clinical, histopathological and cell-cycle markers in rats receiving the fungal toxins fumonisin B1 or fumonisin B2 by intraperitoneal injection.
AUTHOR: Bondy G S(a); Barker M G; Lombaert G A; Armstrong C L; Fernie S M; Gurofsky S; Huzel V; Savard M E; Curran I H A
AUTHOR ADDRESS: (a)Toxicology Research Division, Food Directorate, Health Protection Branch, Health Canada, Ottawa, ON, K1A 0L2**Canada
JOURNAL: Food and Chemical Toxicology 38 (10):p873-886 October, **2000**
MEDIUM: print
ISSN: 0278-6915
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Fumonisins B1 and B2 (FB1 and FB2) are fungal secondary metabolites produced by members of the genus Fusarium. Although FB1 is usually detected in greater quantities, FB2 frequently co-occurs in contaminated feeds and foods and contributes to the total toxin load. In the present study, the comparative toxicity of FB1 and FB2 was examined in male Sprague-Dawley rats administered toxin (0.75 mg/kg body weight) or vehicle control intraperitoneally (ip) for 2, 4 or 6 consecutive days. Clinical changes, including elevated serum cholesterol, alanine aminotransferase (ALT), creatinine and protein, were slightly more pronounced in FB1-treated rats. The most consistent hematological change was an increase in vacuolated bone marrow cells, which was more pronounced in FB1-treated rats. Histopathological changes were similar in FB1- and FB2-treated rats and included single cell necrosis in kidneys and liver, cytoplasmic vacuolation in adrenal cortex and lymphocytolysis in thymus. In the liver mRNA expression for the cyclin kinase inhibitor **p21** gene was significantly increased in FB1- and FB2-treated rats, compared to controls. Expression of mRNA for the cyclin D1 gene was significantly depressed in FB2-treated rats. Hepatic cyclin E mRNA was elevated in response to FB1 and FB2 compared to controls. In FB2-treated animals this corresponded with decreased liver **p27** mRNA expression. Hepatic proliferating cell nuclear antigen (PCNA) transcription was elevated in FB1- but not FB2-treated rats. Changes in liver microsomal protein levels of **p27**, cyclin E and PCNA were similar to changes in gene expression. In contrast, cyclin D1 protein levels were elevated in rats treated with FB1 and, to a lesser extent, FB2. The data indicate that FB1 and FB2 can alter the expression of genes associated with the cell cycle, and indicate a need for a further understanding of the mechanistic basis of FB1 and FB2 toxicity.

2000

20/3,AB/88 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12685814 BIOSIS NO.: 200000439316
Aberrant cell cycle progression contributes to the early-stage accelerated carcinogenesis in transgenic epidermis expressing the dominant negative TGFbetaRII.
AUTHOR: Go Cindy; He Wei; Zhong Ling; Li Ping; Huang Juan; Brinkley Bill R; Wang Xiao-Jing(a)
AUTHOR ADDRESS: (a)Department of Dermatology, Baylor College of Medicine, Houston, TX, 77030**USA
JOURNAL: Oncogene 19 (32):p3623-3631 July, **2000**
MEDIUM: print
ISSN: 0950-9232
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Mutations in the transforming growth factor beta type II receptor (TGFbetaRII) have been found in various malignant tumors, suggesting that loss of TGFbeta signaling plays a causal role in late-stage cancer development. To test whether loss of TGFbetaRII is involved in early-stage carcinogenesis, we have generated transgenic mice expressing a dominant negative TGFbetaRII (DELTAbetaRII) in the epidermis. These mice exhibited an increased susceptibility to chemical carcinogenesis protocols at both early and late stages. In the current study, parameters for cell cycle progression and chromosome instability were analysed in DELTAbetaRII tumors. DELTAbetaRII papillomas showed an increased S phase in flow cytometry. Bromodeoxyuridine (BrdU) labeling and mitotic indices in DELTAbetaRII papillomas also showed a threefold increase compared to papillomas developing in non-transgenic mice. When papillomas further progressed to squamous cell carcinomas (SCC), both control and DELTAbetaRII SCC showed similar BrdU labeling indices and percentage of S phase cells. However, DELTAbetaRII SCC cells showed a sixfold increase in the G2/M population. Mitotic indices in DELTAbetaRII SCC also showed a threefold increase compared to non-transgenic SCC. Consistent with a perturbed cell cycle, DELTAbetaRII papillomas and SCC showed reduced expression of the TGFbeta target genes p15 (INK4b), **p21** (WAF-1) and **p27** (Kip1), inhibitors of cyclin-dependent kinases (cdks). However, most DELTAbetaRII papilloma cells exhibited normal centrosome numbers, and DELTAbetaRII SCC exhibited a similar extent of centrosome abnormalities compared to control SCC (35-40% cells). Most of DELTAbetaRII SCC exhibited diploid chromosome profiles. These data indicate that inactivation of TGFbetaRII accelerates skin tumorigenesis at early stages by the acceleration of loss of cell cycle control, but not by increased chromosome instability.

2000

20/3,AB/89 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12654887 BIOSIS NO.: 200000408389
Functional collaboration between different cyclin-dependent kinase inhibitors suppresses tumor growth with distinct tissue specificity.
AUTHOR: Franklin David S; Godfrey Virginia L; O'Brien Deborah A; Deng Chuxia; Xiong Yue(a)
AUTHOR ADDRESS: (a)Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, 27599-7295**USA

JOURNAL: Molecular and Cellular Biology 20 (16):p6147-6158 August, **2000**
MEDIUM: print
ISSN: 0270-7306
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The presence of two families of seven distinct mammalian cyclin-dependent kinase (CDK) inhibitor genes is thought to mediate the complexity of connecting a variety of cellular processes to the cell cycle control pathway. The distinct pattern of tissue expression of CDK inhibitor genes suggests that they may function as tumor suppressors with different tissue specificities. To test this hypothesis, we have characterized two strains of double mutant mice lacking either p18INK4c and p27KIP1 or p18INK4c and p21CIP1/WAF1. Loss of both p18 and **p27** function resulted in the spontaneous development by 3 months of age of at least eight different types of hyperplastic tissues and/or tumors in the pituitary, adrenals, thyroid, parathyroid, testes, pancreas, duodenum, and stomach. Six of these hyperplastic tissues and tumors were in endocrine organs, and several types of tumors routinely developed within the same animal, a phenotype reminiscent of that seen in combined human multiple endocrine neoplasia syndromes. The p18-**p21** double null mice, on the other hand, developed pituitary adenomas, multifocal gastric neuroendocrine hyperplasia, and lung bronchioalveolar tumors later in life. G1 CDK2 and CDK4 kinase activities were increased in both normal and neoplastic tissues derived from mice lacking individual CDK inhibitors and were synergistically stimulated by the simultaneous loss of two CDK inhibitors. This indicates that an increase in G1 CDK kinase activity is a critical step during but is not sufficient for tumor growth. Our results suggest that functional collaborations between distinct CDK inhibitor genes are tissue specific and confer yet another level of regulation in cell growth control and tumor suppression.

2000

20/3,AB/90 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12650400 BIOSIS NO.: 200000403902
c-fos regulation of cell cycle protein expression in chondrocytes in vitro.
AUTHOR: Gentry A(a); Thomas D P(a); Sunters A(a); Grigoriadis A E(a)
AUTHOR ADDRESS: (a)Dept of Craniofacial Development, King's College London, London**UK
JOURNAL: Journal of Bone and Mineral Research 15 (Suppl. 1):pS468 September, **2000**
MEDIUM: print
CONFERENCE/MEETING: Twenty-Second Annual Meeting of the American Society for Bone and Mineral Research Toronto, Ontario, Canada September 22-26, 2000
SPONSOR: American Society for Bone and Mineral Research
ISSN: 0884-0431
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

20/3,AB/91 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12647558 BIOSIS NO.: 200000401060
Differential association of [redacted]1Cip1 and p27Kip1 with cyclin [redacted]DK2 during **rat** liver regeneration.
AUTHOR: Pujol Maria Jesus; Jaime Maribel; Serratosa Joan; Jaumot Montserrat ; Agell Neus; Bachs Oriol(a)
AUTHOR ADDRESS: (a)Departament de Biologia Cellular, Facultat de Medicina, Universitat de Barcelona, Casanova 143, 08036, Barcelona**Spain
JOURNAL: Journal of Hepatology 33 (2):p266-274 August, **2000**
MEDIUM: print
ISSN: 0168-8278
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Background/Aims: The cell cycle inhibitors p21Cip1 and p27Kip1 regulate liver regeneration by modulating the activity of cyclin-dependent kinases (CDKs). However, the specific role of these inhibitors in the regulation of CDK2 activity during liver regeneration remains unknown. The aim of this study was to examine the association of p21Cip1 and p27Kip1 with cyclin E-CDK2 and cyclin A-CDK2 complexes during **rat** liver regeneration and to correlate the association of both inhibitors with CDK2 activity. Methods: The association of p21Cip1 or p27Kip1 with cyclin E-CDK2 or cyclin A-CDK2 and the activities of these complexes were analyzed by immunoprecipitation of **rat** liver homogenates obtained at different times after a partial hepatectomy (PH), followed by Western blotting or kinase assays. Results: High amounts of p27Kip1 bound to cyclin E-CDK2 were observed during the first 13 h after PH, when CDK2 activity was very low. At 24 h, when CDK2 activity was maximal, the amount of bound-p27Kip1 decreased strongly. The amount of p21Cip1 bound to these complexes was low during the first 13 h but subsequently increased. No cyclin A-CDK2 complexes were found during the first 13 h after PH. At 24 h, complexes containing low levels of both inhibitors were detected and at 28 h, a significant increase in p21Cip1 and p27Kip1 associated with cyclin A-CDK2 was observed. Conclusions: p27Kip1 acts as a brake on cyclin E-CDK2 activity during the first 13 h after a PH. Both p21Cip1 and p27Kip1 down-regulate cyclin A-CDK2 activity at 28 h after PH, after its maximal activation.

2000

20/3,AB/92 (Item 17 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12635207 BIOSIS NO.: 200000388709
Regulation of cell cycle proteins by TNF-alpha and TGF-beta in cells of oligodendroglial lineage.
AUTHOR: Yu Chao; Takeda Margaret; Soliven Betty(a)
AUTHOR ADDRESS: (a)Department of Neurology, Brain Research Institute, University of Chicago, Chicago, IL, 60637**USA
JOURNAL: Journal of Neuroimmunology 108 (1-2):p2-10 August 1, **2000**
MEDIUM: print
ISSN: 0165-5728
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Proliferation and apoptosis are two dynamic, interrelated processes that are regulated by growth factors and cytokines. We investigated the effects of tumor necrosis factor-alpha (TNF-alpha) and transforming growth factor-beta (TGF-beta) on apoptosis and regulation of cell cycle proteins in OLG lineage cells. We found that: (1) both

cytokines enhanced apoptosis in neonatal pre-OLGs but only TNFalpha-mediated apoptosis persisted in the presence of a mitogen, fibroblast growth factor (FGF); (2) cell cycle proteins such as p21waf1/cip1, p27kip1, cyclin D1 and PCNA were differentially regulated by TNF-alpha and TGF-beta. We conclude that differential modulation of cell cycle proteins by TNF-alpha and TGF-beta contributes to the diversity of their biological effects in OLG lineage cells.

2000

20/3,AB/93 (Item 18 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12631404 BIOSIS NO.: 200000384906
Friend virus-induced erythroblastosis in Stat5a/b mutant mice: Properties of isolated erythroblasts in vitro.
AUTHOR: Bondurant Maurice(a); Ney Paul; Gregoli Paul; Tian Cuixia
AUTHOR ADDRESS: (a)Veterans Affairs Medical Center, Nashville, TN**USA
JOURNAL: Experimental Hematology (Charlottesville) 28 (7 Supplement 1):p 44-45 July, **2000**
MEDIUM: print
CONFERENCE/MEETING: 29th Annual Meeting of the International Society for Experimental Hematology Tampa, Florida, USA July 08-11, 2000
SPONSOR: International Society for Experimental Hematology
ISSN: 0301-472X
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

20/3,AB/94 (Item 19 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12562932 BIOSIS NO.: 200000316434
Prolonged STAT3 activation inhibits hepatocyte proliferation after hepatectomy.
AUTHOR: Wuestefeld T; Rakemann T; Kubicka S; Manns M P; Trautwein C
AUTHOR ADDRESS: (a)Gastroenterology and Hepatology, Medical School Hannover, Hannover**Germany
JOURNAL: Journal of Hepatology 32 (Supplement 2):p161 **2000**
MEDIUM: print
CONFERENCE/MEETING: 35th Annual Meeting of the European Association for the Study of the Liver Rotterdam, Netherlands April 29-May 03, 2000
SPONSOR: European Association for the Study of the Liver
ISSN: 0168-8278
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

20/3,AB/95 (Item 20 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12562794 BIOSIS NO.: 200000316296
p21 (WAF1/CIP1) is required for the mitogenic response to intestinal resection.
AUTHOR: Stern Lawrence E; Falcone Richard A Jr; Kemp Christopher J; Erwin Christopher R; Warner Brad W
AUTHOR ADDRESS: (a)Division of Pediatric Surgery, Children's Hospital

Medical Center, 3333 Burnet Avenue, Cincinnati, OH, 45229-3039**USA
JOURNAL: Journal of Surgical Research 90 (1):p45-50 May 1, 0
MEDIUM: print
ISSN: 0022-4804
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Background: Increased enterocyte proliferation and apoptosis characterize the intestinal adaptive response to massive small bowel resection (SBR). Since **p21** (WAF1/CIP1) has been implicated to play a role in cellular differentiation and apoptosis, this study tested the hypothesis that **p21** is obligatory for adaptation to occur. Materials and methods: **p21**-null (n = 36) and wild-type (C57B1/6, n = 19) mice underwent a 50% SBR or sham operation. After 3 days, parameters of adaptation (ileal wet weight, villus/crypt morphology, and ileal protein content), an enterocyte proliferation index (PI), and an apoptotic index (AI) were determined in the residual ileum. In a separate set of experiments, **p21**-null (n = 11) and control (n = 20) mice underwent the aforementioned operative procedures and the remnant intestine was subjected to a reverse transcription polymerase chain reaction for **p27** (KIP1). Results: Both AI and PI increased after SBR in the wild-type mice. In the **p21**-null mice, SBR increased AI, but did not affect the PI. After SBR, adaptive parameters increased in the wild-type mice, but failed to increase in the **p21**-null mice. The absence of **p21** caused a baseline increase in **p27** mRNA, which did not change after SBR. Conclusion: **p21** appears to be required to increase enterocyte proliferation and to augment the other parameters of intestinal adaptation. In the absence of **p21**, the proliferative and apoptotic responses to SBR are uncoupled. These results suggest a differential mechanism for the regulation of enterocyte proliferation and apoptosis in the adapting intestine.

2000

20/3,AB/96 (Item 21 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12553778 BIOSIS NO.: 200000307280
In acute hepatic failure rats inhibition of liver growth is associated with up-regulation of p21WAF1, CIP1, SDI1 and p27KIP1.
AUTHOR: Mizuguchi T; Hui T; Sugiyama N; Navarro R A; Ting P; Neuman T; Demetriou A A; Rozga J
AUTHOR ADDRESS: (a)Liver Support Research Laboratory, Dept. of Surgery, Cedars-Sinai Medical Center, UCLA School of Medicine, Los Angeles, CA, 90048**USA
JOURNAL: FASEB Journal 14 (4):pA175 March 15, **2000**
MEDIUM: print
CONFERENCE/MEETING: Annual Meeting of Professional Research Scientists: Experimental Biology 2000 San Diego, California, USA April 15-18, 2000
SPONSOR: Federation of American Societies for Experimental Biology
ISSN: 0892-6638
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

20/3,AB/97 (Item 22 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12543099 BIOSIS NO.: 200000296601

Hepatocyte growth factor (HGF) inhibits skeletal muscle cell differentiation: A role for the bHLH protein twist and the cell cycle inhibitor **p27**.

AUTHOR: Leshem Yael; Spicer Douglas B; Gal-Levi Ronit; Halevy Orn
AUTHOR ADDRESS: (a)Dept. of Animal Sciences, Hebrew University of Jerusalem, Rehovot, 76100**Israel

JOURNAL: Journal of Cellular Physiology 184 (1):p101-109 July, **2000**
MEDIUM: print
ISSN: 0021-9541
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Hepatocyte growth factor (HGF) plays a crucial role in regulating the differentiation of both fetal and adult skeletal myoblasts. This study aimed at defining the intracellular factors that mediate the effect of HGF on adult myoblast differentiation. HGF increased Twist expression while decreasing p27kip1 protein levels and not affecting the induction of p21Cip1/Waf1 in satellite cells. Like HGF, overexpression of Twist did not affect **p21** expression while inhibiting muscle-specific proteins. Both ectopic Twist-antisense (Twist-AS) and **p27** partially rescued the effects of HGF on bromodeoxyuridine (BrdU) incorporation and myosin heavy chain (MHC) expression in muscle satellite cells; the two plasmids together effected full rescue, suggesting that HGF independently regulates these two factors to mediate its effects. Ectopic **p27** promoted differentiation in the presence of HGF by blocking the induction of Twist. Using Twist-AS to lower Twist levels restored the HGF-dependent reduction of **p27** and MHC. In the presence of ectopic HGF, satellite cells formed thin mononuclear myotubes. Neither ectopic **p27**, Twist-AS, or their combination reversed this change in cell morphology, suggesting that HGF acts through additional mediators to inhibit downstream events during myogenesis. Taken together, the results suggest that the effects of HGF on muscle cell proliferation and differentiation are mediated through changes in the expression levels of the myogenic-inhibitory basic helix-loop-helix (bHLH) protein Twist and the cell-cycle inhibitor **p27**.

2000

20/3,AB/98 (Item 23 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12519548 BIOSIS NO.: 200000273050
Two novel 14-epi-analogues of 1,25-dihydroxyvitamin D3 inhibit the growth of human breast cancer cells in vitro and in vivo.

AUTHOR: Verlinden Lieve; Verstuyf Annemieke; Van Camp Mark; Marcelis Suzanne; Sabbe Katrien; Zhao Xu-Yang; De Clercq Pierre; Vandewalle Maurits; Bouillon Roger(a)
AUTHOR ADDRESS: (a)LEGENDO Onderwijs en Navorsing, Gasthuisberg, 3000, Leuven**Belgium

JOURNAL: Cancer Research 60 (10):p2673-2679 May 15, **2000**
MEDIUM: print.
ISSN: 0008-5472
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The biological activity of two novel 14-epi-analogues of 1,25(OH)2D3, 19-nor-14-epi-23-yne-1,25(OH)2D3 (TX 522) and 19-nor-14,20-bisepi-23-yne-1,25(OH)2D3 (TX 527), is described. Both analogues were at least 10 times more potent than 1,25(OH)2D3 in

inhibiting in vitro cell proliferation and had much lower in vivo calcemic effects than 1,25(OH)2D3. Treatment with 1,25(OH)2D3, TX 522, or TX 527 in vitro was accompanied by an accumulation of cells in the G1 phase of the cell cycle. Protein levels of cyclin C and cyclin D1 in in vitro cultures of MCF-7 cells were down-regulated to 50 and 30%, respectively, of control levels at 72 and 120 h after stimulation. Protein levels of **p21** and **p27** at 72 h were significantly enhanced by 1,25(OH)2D3 and TX 522 but surprisingly not by TX 527. The inability of TX 527 to up-regulate **p21** seemed to be cell type specific because **p21** was induced in other cell types. Diminished phosphorylation of the retinoblastoma protein after treatment with 1,25(OH)2D3, TX 522, or TX 527 may ultimately contribute to the growth inhibition caused by these compounds. According to the data presented, the induction of apoptosis seemed not to be a major mechanism responsible for the growth-inhibitory effect of 1,25(OH)2D3 and analogues. Both 14-epi-analogues significantly retarded tumor progression (40% reduced compared with control mice) in an in vivo model of MCF-7 breast cancer cells established in nude mice. In conclusion, these novel analogues have the eligible profile to be tested as therapeutic agents for the treatment of hyperproliferative diseases such as breast cancer.

2000

20/3,AB/99 (Item 24 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12515524 BIOSIS NO.: 200000269026
Transfection of a mutated ki-ras cDNA into SV40 immortalized pancreatic duct cell leads to malignant transformation.
AUTHOR: Jesnowski Ralf(a); Schmidt Christian(a); Liebe Stefan(a); Lshr Matthias(a)
AUTHOR ADDRESS: (a)Univ of Rostock, Rostock**Germany
JOURNAL: Gastroenterology 118 (4 Suppl. 2 Part 2):pAGA A1147 April, **2000**
MEDIUM: print.
CONFERENCE/MEETING: 101st Annual Meeting of the American Gastroenterological Association and the Digestive Disease Week. San Diego, California, USA May 21-24, 2000
SPONSOR: American Gastroenterological Association
ISSN: 0016-5085
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

20/3,AB/100 (Item 25 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12508672 BIOSIS NO.: 200000262174
Anti-neoplastic effects of proteasome inhibitor MG-132.
AUTHOR: Shao Jinyi(a); Sheng Hongmiao(a); Helou Rania A(a); DuBois Raymond N(a)
AUTHOR ADDRESS: (a)Vanderbilt Med Ctr, Nashville, TN**USA
JOURNAL: Gastroenterology 118 (4 Suppl. 2 Part 1):pAGA A525 April, **2000**
MEDIUM: print.
CONFERENCE/MEETING: 101st Annual Meeting of the American Gastroenterological Association and the Digestive Disease Week. San Diego, California, USA May 21-24, 2000
SPONSOR: American Gastroenterological Association
ISSN: 0016-5085

RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

20/3,AB/101 (Item 26 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12474792 BIOSIS NO.: 200000228294
Mouse lymphocytes deficient for both p21Cip1 and p27Kip1 retain sensitivity to TGF-beta mediated growth arrest: Evidence for multiple pathways.
AUTHOR: Wolfraim Lawrence A(a); Walz Thomas M; Anver Miriam R; Koff Andrew; Letterio John J
AUTHOR ADDRESS: (a)Dept of Biomed and Surg, Linkoping Univ, Linkoping** Sweden
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting (41):p561 March, **2000**
CONFERENCE/MEETING: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA April 01-05, 2000
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

20/3,AB/102 (Item 27 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12463205 BIOSIS NO.: 200000216707
Use of 12-O-tetradecanoylphorbol-13-acetate (TPA) induced proliferation in the **mouse** skin to evaluate cell cycle inhibitors.
AUTHOR: Webster Kevin R(a); Dell J(a); Ho C-P(a); Mulheron J G(a); Bol D K (a)
AUTHOR ADDRESS: (a)Bristol-Myers Squibb Pharm Res Institute, Princeton, NJ **USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting (41):p471-472 March, **2000**
CONFERENCE/MEETING: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA April 01-05, 2000
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

20/3,AB/103 (Item 28 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12462946 BIOSIS NO.: 200000216448
Infection with adenovirus E1B defectives exerts a marked cytopathic effect on mice cells deficient in p16, **p21**, **p27** or p53 genes.
AUTHOR: Duque P Martin(a); Quintanilla M(a); Guinea J(a); Martinez A(a); Ramon y Cajal S(a)
AUTHOR ADDRESS: (a)Inst de Invest Biomed, Clinica Puerta de Hierro, Madrid **Spain
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting (41):p455 March, **2000**
CONFERENCE/MEETING: 91st Annual Meeting of the American Association for

Cancer Research. San Francisco, California, USA April 01-05, 2000
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

20/3,AB/104 (Item 29 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12452154 BIOSIS NO.: 200000205656
Mechanism of hepatocyte proliferation in p53 knockout and mutant mice.
AUTHOR: Yang Chuanwei(a); Friedrich Thomas(a); Sell Stewart(a)
AUTHOR ADDRESS: (a)Albany Med Coll, Albany, NY**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting (41):p119 March, **2000**
CONFERENCE/MEETING: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA April 01-05, 2000
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

20/3,AB/105 (Item 30 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12452153 BIOSIS NO.: 200000205655
Rapid induction of cyclin D1 expression by the mitogen TCPOBOP is associated with an accelerated entry into S phase of **rat** hepatocytes.
AUTHOR: Columbano Amedeo(a); Pibiri Monica(a); Loi Roberto(a); Perra Andrea (a); Shinozuka Hisashi(a); Ledda-Columbano Giovanna Maria(a)
AUTHOR ADDRESS: (a)Univ, Cagliari, Cagliari**Italy
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting (41):p117 March, **2000**
CONFERENCE/MEETING: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA April 01-05, 2000
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

20/3,AB/106 (Item 31 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12393646 BIOSIS NO.: 200000147148
Adenovirus-mediated ectopic expression of cyclin kinase inhibitors p16ink4a, p21clp and p27kipl in murine cortical precursors cells.
AUTHOR: Lukaszewicz A(a); Savatier P; Cortay V(a); Seth P; Kennedy H(a); Dehay C(a)
AUTHOR ADDRESS: (a)INSERM U 371, 18 Ave. Doyen Lepine, 69675, Bron**France
JOURNAL: Society for Neuroscience Abstracts. 25 (1-2):p1540 **1999**
CONFERENCE/MEETING: 29th Annual Meeting of the Society for Neuroscience. Miami Beach, Florida, USA October 23-28, 1999
SPONSOR: Society for Neuroscience
ISSN: 0190-5295
RECORD TYPE: Citation

LANGUAGE: English
SUMMARY LANGUAGE: English
1999

20/3,AB/107 (Item 32 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12335559 BIOSIS NO.: 200000089061
Cyclin kinase inhibitor p21CIP1/WAF1 limits interstitial cell proliferation following ureteric obstruction.
AUTHOR: Hughes Jeremy(a); Brown Paul; Shankland Stuart J
AUTHOR ADDRESS: (a)Division of Nephrology, University of Washington, Seattle, WA, 98195-6521**USA
JOURNAL: American Journal of Physiology 277 (6 part 2):pF948-F956 Dec., **1999**
ISSN: 0002-9513
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Tubulointerstitial renal injury induced by unilateral ureteric obstruction (UUO) is characterized by marked cell proliferation and apoptosis. Proliferation requires cell cycle transit that is positively regulated by cyclins and cyclin-dependent kinases (CDKs) and inhibited by the CIP/KIP family of cyclin-dependent kinase inhibitors (CKIs: **p21**, **p27**, and p57). We have shown that the absence of **p27** results in markedly increased tubular epithelial cell proliferation and apoptosis following UUO (V. Ophascharoensuk, M. L. Fero, J. Hughes, J. M. Roberts, and S. J. Shankland. Nat. Med. 4: 575-580, 1998). Since **p21** mRNA is upregulated following UUO, we hypothesized that **p21** would also serve to limit cell proliferation and apoptosis. We performed UUO in **p21** +/+ and **p21** -/- mice. Cell proliferation (bromodeoxyuridine (BrdU), proliferating cell nuclear antigen (PCNA)), apoptosis (terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling (TUNEL) method), interstitial myofibroblast accumulation (actin), macrophage infiltration (F4/80), and collagen I expression were quantified at days 3, 7, and 14. In contrast to **p27** -/- mice, there was no difference in tubular epithelial cell proliferation or apoptosis between **p21** -/- and **p21** +/+ mice at any time point. However, interstitial cell proliferation at day 3 was significantly increased in **p21** -/- mice (BrdU, 40.7 +- 1.9 cells/high-power field (cells/hpf) vs. 28.8 +- 2, $P < 0.005$), although, interestingly, no difference was seen in interstitial cell apoptosis. Actin/BrdU double staining demonstrated increased interstitial myofibroblast proliferation at day 3 in **p21** -/- animals (10 +- 0.12 vs. 5.8 +- 0.11 cells/hpf, $P < 0.05$), which was followed by increased myofibroblast accumulation at day 7 in **p21** -/- mice. No differences were detected in interstitial macrophage infiltration, collagen I deposition or transforming growth factor-betal mRNA (in situ hybridization) expression. In conclusion **p21**, unlike **p27**, is not essential for the regulation of tubular epithelial cell proliferation and apoptosis following UUO, but **p21** levels do serve to limit the magnitude of the early myofibroblast proliferation. This study demonstrates a differential role for the CKI **p21** and **p27** in this model.

1999

20/3,AB/108 (Item 33 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12301894 BIOSIS NO.: 200[redacted]59761
Effect of elevated levels of ornithine decarboxylase on cell cycle progression in skin.
AUTHOR: Gilmour Susan K(a); Birchler Mary; Smith Mary K; Rayca Kathryn; Mostochuk Judith
AUTHOR ADDRESS: (a)Lankenau Medical Research Center, 100 Lancaster Avenue, Wynnewood, PA**USA
JOURNAL: Cell Growth & Differentiation 10 (11):p739-748 Nov., **1999**
ISSN: 1044-9523
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: By crossing TG.AC v-Ha-ras and K6/ODC transgenic mice, we found previously that an activated ras and follicular ornithine decarboxylase (ODC) overexpression cooperate to generate spontaneous tumors in the skin. Cellular proliferation was dramatically increased in the K6/ODC transgenic skin, as evidenced by elevated proliferating cell nuclear antigen and Ki67 expression compared with nontransgenic littermates. Keratinocytes isolated from transgenic skin also displayed increased clonal growth. Paradoxically, expression of the growth inhibition-associated proteins p53, p21Waf1, p27Kip1, and Bax was increased with ODC overexpression in the skin. ODC overexpression did not affect cyclin D/cyclin-dependent kinase 4 (Cdk4)-dependent phosphorylation of retinoblastoma protein but stimulated cyclin E/Cdk2 and cyclin A/Cdk2-associated kinase activity, with minimal effect on the levels of these proteins. Thus, ODC/polyamine-induced activation of cyclin E/Cdk2 and cyclin A/Cdk2-associated kinase activity may cooperate with the ras induction of cyclin D/Cdk4/6-associated retinoblastoma protein phosphorylation to not only stimulate proliferation but ultimately contribute to tumor development.

1999

20/3,AB/109 (Item 34 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12292288 BIOSIS NO.: 200000050155
Growth induction of **rat** primary hepatocytes using antisense oligonucleotides.
AUTHOR: Hamamoto Ryuji; Seko Hirofumi; Kamimura Ryosuke; Yamada Keisuke; Murai Kiyohito; Kamihira Masamichi(a); Iijima Shinji
AUTHOR ADDRESS: (a)Department of Biotechnology, Graduate School of Engineering, Nagoya University, Chikusa-ku, Nagoya, 464-8603**Japan
JOURNAL: Journal of Bioscience and Bioengineering 88 (3):p310-315 Sept., **1999**
ISSN: 1389-1723
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: We examined growth control of adult and fetal hepatocytes by regulating the expression of cell-cycle-related proteins using antisense S-oligonucleotides to tumor suppressors retinoblastoma (RB) protein and p53, and cyclin-dependent kinase (CDK) inhibitors **p21** and **p27** . The protein expression in both adult and fetal hepatocytes was significantly suppressed with the addition of corresponding antisense oligonucleotides at a concentration of 2.5 muM. For the evaluation of growth, 3H-thymidine incorporation and DNA content were measured and the results demonstrated that all the antisense oligonucleotides had

growth-promoting effects and the promoting potential was equivalent or slightly greater than that with the addition of hepatocyte growth factor (HGF) (10 ng/ml). The growth-promoting effect of the antisense oligonucleotides was enhanced by HGF in both adult and fetal hepatocyte cultures, and the effects on hepatocyte growth were also observed in a suspension culture.

1999

20/3,AB/110 (Item 35 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12279696 BIOSIS NO.: 200000033198
Prostate cancer cell cycle regulators: Response to androgen withdrawal and development of androgen independence.
AUTHOR: Agus David B(a); Cordon-Cardo Carlos; Fox William; Drobnjak Marija; Koff Andrew; Golde David W; Scher Howard I
AUTHOR ADDRESS: (a)Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021**USA
JOURNAL: Journal of the National Cancer Institute (Bethesda) 91 (21):p 1869-1876 Nov. 3, **1999**
ISSN: 0027-8874
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Background: Androgen withdrawal is a standard therapy for prostate cancer that results in a decrease in tumor volume and a decline in serum prostate-specific antigen in the majority of patients. To understand the factors associated with regression of prostate cancers after androgen withdrawal, we studied cell cycle regulator changes in the CWR22 human prostate cancer xenograft model. Methods: Established tumors in nude athymic BALB/c mice were sampled at various times after androgen withdrawal and after the development of androgen independence. Changes in the expression of cell cycle regulators were categorized into early and mid-to-late events. Results and Conclusions: Early events included a decrease in androgen receptor expression, followed by a short-term increase in expression of the p53 and **p21**/WAF1 proteins and a marked decrease in the Ki67 proliferative index. Mid-to-late events included progressive and sustained increases in **p27** and p16 protein expression, a decrease in retinoblastoma protein expression, and an increase in the transcription factor E2F1. Changes in apoptosis (programmed cell death) were not observed at any time after androgen withdrawal. These data suggest that androgen withdrawal results in a cell stress response, in which increased p53 protein produces a cell cycle arrest, without activation of p53-mediated apoptosis. The proliferative index is further decreased through the action of the cyclin-dependent kinase inhibitors **p27** and p16. Androgen-independent sublines emerged 80-400 days after androgen withdrawal, and these sublines had variable growth phenotypes but were associated with mdm2 protein overexpression and increased expression of cyclin D1. These results indicate that tumor regression in this human prostate cancer model is due to cell cycle arrest rather than to apoptosis and that the emergence of androgen independence is associated with a release from cell cycle arrest.

1999

20/3,AB/111 (Item 36 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12271881 BIOSIS NO.: 2000[redacted]25383
CDK-inhibitor independent cell cycle progression in an experimental haematopoietic stem cell leukaemia despite unaltered Rb-phosphorylation.
AUTHOR: Huss R(a); Theis S; Deeg H J
AUTHOR ADDRESS: (a)Institute of Pathology, University of Munich, Thalkirchner Str. 36, D-80337, Munich**Germany
JOURNAL: British Journal of Cancer 81 (5):p808-813 Nov., **1999**
ISSN: 0007-0920
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: A CD34-negative haematopoietic progenitor cell line, D064, derived from canine bone marrow stromal cells is able to differentiate into haematopoietic progenitors under the influence of growth factor-mediated signalling. While differentiating, these cells eventually start to express MHC class II molecules (DR homologues) on their surface. The stable transfection of the fibroblast-like wild-type cells with retroviral constructs containing the cDNA for the canine MHC class II DR-genes (DRA and DRB) induces a change in morphology, accelerates cell cycle progression and leads to a loss of anchorage-dependent growth. Transfected cells show features of an immature stem cell leukaemia, such as giant cell formation. In wild-type D064 cells the accumulation of the cyclin-dependent kinase inhibitor (cdki) p27kip-1 induces differentiation, which is dependent upon signalling via the ligand for the tyrosine kinase receptor c-kit (stem cell factor). DR-transfected cells instead apparently grow i ndependently of any growth factor-mediated signals and express high levels of the cdkis p27kip-1 and especially p21waf-1/cip-1, concurrently with accelated cell cycle progression. In contrast to the overexpression of cdkis and despite accelerated cell cycle progression, the expression of the G2/M phase transition kinase p34cdc2 is significantly reduced in DR-transfected and transformed cells as compared to the haematopoietic wild-type cell line D064. This might suggest a possible alternative cell cycle progression pathway in this experimental stem cell leukaemia by by-passing the G0/G1 phase arrest, although retinoblastoma (Rb)-phosphorylation remains unaltered. These results provide evidence that mechanisms normally controlling the cell cycle and early haematopoietic differentiation are disrupted by the constitutive transcription and expression of MHC class II genes (DR) leading to a progression and growth of this experimental stem cell leukaemia independent from c ell cycle controlling regulators such as **p27** and **p21**.

1999

20/3,AB/112 (Item 37 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12249285 BIOSIS NO.: 200000002787
Calcitonin receptor-mediated growth suppression of HEK-293 cells is accompanied by induction of p21WAF1/CIP1 and G2/M arrest.
AUTHOR: Evdokiou Andreas(a); Raggatt Liza-Jane; Atkins Gerald J; Findlay David M
AUTHOR ADDRESS: (a)Department of Orthopaedics and Trauma, University of Adelaide, Adelaide, SA, 5000**Australia
JOURNAL: Molecular Endocrinology 13 (10):p1738-1750 Oct., **1999**
ISSN: 0888-8809
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: We investigated t[redacted]mechanisms by which calcitonin[redacted]T) suppresses cellular proliferation, using HEK-293 cells stably transfected with either the **rat** C1a CT receptor (CTR) or the insert-negative form of the human CTR. CT treatment of clonal cell lines expressing either receptor type, but not untransfected HEK-293 cells, strongly suppressed cell growth in a concentration-dependent manner. The reduction in cell growth with CT treatment could not be attributed to cellular necrosis or apoptotic cell death, the latter assessed by both DNA fragmentation analysis and caspase 3 (CPP-32) assay. Growth inhibition was associated with an accumulation of cells in the G2 phase of the cell cycle. CT treatment of the human and **rat** CTR-expressing cell lines resulted in a rapid and sustained induction of mRNA encoding the cyclin-dependent kinase inhibitor, p21WAF1/CIP1, increased levels of which were maintained at least 48 h after initiation of treatment. Western blot analysis showed a rapid c orresponding increase in p21WAF1/CIP1 protein, whereas protein levels of another member of the cyclin-dependent kinase inhibitor family, p27kip1, were unchanged. In parallel with the induction of **p21**, CT treatment reduced levels of p53 mRNA and protein. CT treatment resulted in a specific cell cycle block in G2, which was associated with inhibition of Cdc2/cyclin B kinase activity as measured by histone H1 phosphorylation. There was no evidence for **p21** association with this complex despite the inhibition of Cdc2 activity. Evidence that **p21** induction was causative of cell growth suppression was obtained from **p21** antisense oligonucleotide experiments. Treatment with a **p21** antisense oligonucleotide blocked induction of **p21** expression and significantly reduced the CT-mediated growth inhibition. These observations suggest that **p21** is required for the G2 arrest in response to CT, but argue against a direct role of **p21** in the inhibition of Cdc2 activity. These studies suggest a novel regulation of cell cycle progression by CT and will provide a basis for detailed examination of the molecular mechanisms involved.

1999

20/3,AB/113 (Item 38 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12234421 BIOSIS NO.: 199900529270
Cytosolic phospholipase A2 regulates mesangial cell proliferation by modulating expression of p27Kip1 and p21Cip1.
AUTHOR: Choukroun Gabriel(a); Force Thomas(a); Alessandrini Alessandro(a); Sun Xiao-Ming(a); Bonventre Joseph V(a)
AUTHOR ADDRESS: (a)Renal Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA**USA
JOURNAL: Journal of the American Society of Nephrology 10 (PROGRAM AND ABSTR. ISSUE):p467A Sept., **1999**
CONFERENCE/MEETING: 32nd Annual Meeting of the American Society of Nephrology Miami Beach, Florida, USA November 1-8, 1999
SPONSOR: American Society of Nephrology
ISSN: 1046-6673
RECORD TYPE: Citation
LANGUAGE: English
1999

20/3,AB/114 (Item 39 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12229193 BIOSIS NO.: 199900524042
Adenoviral delivery of iNOS inhibits VSMC proliferation through cell cycle

control.
AUTHOR: Kibbe Melina R; Bi[redacted]r Timothy R; Tzeng Edith
AUTHOR ADDRESS: Univ. Pittsburgh, Pittsburgh, PA**USA
JOURNAL: Circulation 98 (17 SUPPL.):pI388 Oct. 27, **1998**
CONFERENCE/MEETING: 71st Scientific Sessions of the American Heart Association Dallas, Texas, USA November 8-11, 1998
SPONSOR: The American Heart Association
ISSN: 0009-7322
RECORD TYPE: Citation
LANGUAGE: English
1998

20/3,AB/115 (Item 40 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12212642 BIOSIS NO.: 199900507491
E2F-1 induces cell cycle reentry in cardiomyocytes through release of kip1/cip cdk inhibitors.
AUTHOR: Hauck Ludger; Mehrhof Felix; Cardoso Cristina; Von Harsdorf Ruediger
AUTHOR ADDRESS: Humboldt-Univ., Berlin**Germany
JOURNAL: Circulation 98 (17 SUPPL.):pI262 Oct. 27, **1998**
CONFERENCE/MEETING: 71st Scientific Sessions of the American Heart Association Dallas, Texas, USA November 8-11, 1998
SPONSOR: The American Heart Association
ISSN: 0009-7322
RECORD TYPE: Citation
LANGUAGE: English
1998

20/3,AB/116 (Item 41 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12167171 BIOSIS NO.: 199900462020
Expression of cyclin-dependent kinase inhibitors (p27KIP1, p21WAF1, p16INK4A, p15INK4B) during osteoclast differentiation.
AUTHOR: Woo K M(a); Ko S H(a); Ko J S
AUTHOR ADDRESS: (a)College of Dentistry, Kangnung National University, Kangnung**South Korea
JOURNAL: Journal of Bone and Mineral Research 14 (SUPPL. 1):pS485 Sept., **1999**
CONFERENCE/MEETING: Twenty-First Annual Meeting of the American Society for Bone and Mineral Research St. Louis, Missouri, USA September 30-October 4, 1999
SPONSOR: American Society for Bone and Mineral Research
ISSN: 0884-0431
RECORD TYPE: Citation
LANGUAGE: English
1999

20/3,AB/117 (Item 42 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12160693 BIOSIS NO.: 199900455542
Tumor suppression by p27Kip1 and p21Cip1 during chemically induced skin carcinogenesis.
AUTHOR: Philipp Jeannette; Vo Khoa; Gurley Kay E; Seidel Kristy; Kemp Christopher J(a)
AUTHOR ADDRESS: (a)Fred Hutchinson Cancer Research Center, 1100 Fairview

N., Seattle, WA, 98109**USA
JOURNAL: Oncogene 18 (33) [redacted]89-4698 Aug. 19, **1999**
ISSN: 0950-9232
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: p27Kip1 and p21Cip1 are cyclin dependent kinase inhibitors which can arrest cell proliferation and **p27** is a tumor suppressor gene. To address the mechanism of tumor suppression by **p27** and to determine if **p21** has a tumor suppressor phenotype, we utilized the two stage skin carcinogenesis model on **p27** and **p21** knockout mice. In this model, initiation, which involves mutation of H-ras induced by DMBA, can be distinguished from promotion induced by TPA, and progression to carcinoma. The mean number of papillomas did not differ between **p27** - / - and control littermates, but papilloma growth rate was increased and carcinomas developed earlier. Thus, **p27** deficiency did not enhance initiation, but resulted in more rapid clonal expansion of initiated cells during promotion. TPA treatment reduced **p27** expression in keratinocytes also supporting a role for **p27** during promotion. Tumors from **p27** - / - mice contained mutant H-ras indicating that **p27** deficiency did not substitute for mutant rasand further, that during ras driven tumor growth, **p27** is partially antagonistic since its removal led to faster growth. The treated **p27** - / - mice also developed intestinal adenomas. **p21** - / - mice did not display a significant increase in tumor numbers, growth rate or progression to carcinomas and these tumors also had mutated H-ras. Carcinomas from **p21** - / - mice were more poorly differentiated with a high frequency of anaplastic spindle cell carcinomas. Thus **p21** deficiency mainly resulted in higher grade undifferentiated tumors.

1999

20/3,AB/118 (Item 43 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12140230 BIOSIS NO.: 199900435079
Inhibition of gastric cancer by camptothecin involves apoptosis and multiple cellular pathways.
AUTHOR: Litvak David A; Papaconstantinou Harry T; Hwang Kevin O; Kim Mimi; Evers B Mark(a); Townsend Courtney M Jr
AUTHOR ADDRESS: (a)Department of Surgery, University of Texas Medical Branch, 301 University Blvd, Galveston, TX, 77555-0533**USA
JOURNAL: Surgery (St Louis) 126 (2):p223-230 Aug., **1999**
ISSN: 0039-6060
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Background. The prognosis for gastric cancer remains dismal; novel agents that target specific molecular pathways are needed as adjuvant therapy. Camptothecin (CPT), an inhibitor of topoisomerase I, is effective in the treatment of certain solid tumors; its effects on gastric cancer are largely undefined. The purpose of this study was to (1) characterize the effects of CPT on the growth of a human gastric cancer and (2) assess potential cellular mechanisms responsible for CPT-mediated growth inhibition. Methods. The human gastric cancer SIIA was transplanted subcutaneously into athymic nude mice. After tumors reached apprx100 mm2, mice were randomized into 3 groups to receive either CPT (5 or 10 mg/kg) or vehicle (control) intraperitoneally 3 days

per week for 3 weeks; tumor size was measured biweekly. To assess potential mechanisms of CPT-mediated inhibition, SIIA cells were treated with CPT (20 mumol/L) and cells were counted over a time course; apoptosis was assessed by Hoechst stainand DNA laddering. Expression of p53 (a tumor suppressor), p21Waf1 and p27Kip1 (cell cycle inhibitors), and Bcl-2 and Bcl-XL (antiapoptotic proteins) was determined. Results. CPT (5 and 10 mg/kg) significantly inhibited tumor growth of SIIA gastric cancers compared with controls. CPT-mediated inhibition of SIIA cell proliferation was associated with an increase in apoptosis. Moreover, CPT treatment resulted in induction of p53, p21Waf1, and p27Kip1 and a decrease in Bcl-2 and Bcl-XL RNA and protein levels. Conclusions. Treatment with CPT effectively inhibited the growth of the human gastric cancer SIIA; the mechanism involved was induction of apoptosis mediated by up-regulation of p53, p21Waf1/Cip1, and p27Kip1 and the down-regulation of Bcl-2 and Bcl-XL. Novel agents such as CPT, which target specific molecular pathways, may prove clinically useful in the adjuvant treatment of gastric cancers.
1999

20/3,AB/119 (Item 44 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12037838 BIOSIS NO.: 199900318357
Voltage-activated K+ channels and membrane depolarization regulate accumulation of the cyclin-dependent kinase inhibitors p27Kip1 and p21CIP1 in glial progenitor cells.
AUTHOR: Ghiani Cristina A; Yuan Xiaoqing; Eisen Alex M; Knutson Peter L; DePinho Ronald A; McBain Chris J; Gallo Vittorio(a)
AUTHOR ADDRESS: (a)Laboratory of Cellular and Molecular Neurophysiology, National Institute of Child Health and Hum**USA
JOURNAL: Journal of Neuroscience 19 (13):p5380-5392 July 1, **1999**
ISSN: 0270-6474
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Neural cell development is regulated by membrane ion channel activity. We have previously demonstrated that cell membrane depolarization with veratridine or blockage of K+ channels with tetraethylammonium (TEA) inhibit oligodendrocyte progenitor (OP) proliferation and differentiation (Knutson et al., 1997); however the molecular events involved are largely unknown. Here we show that forskolin (FSK) and its derivative dideoxyforskolin (DFSK) block K+ channels in OPs and inhibit cell proliferation. The antiproliferative effects of TEA, FSK, DFSK, and veratridine were attributable to OP cell cycle arrest in G1 phase. In fact, (1) cyclin D accumulation in synchronized OP cells was not affected by K+ channel blockers or veratridine; (2) these agents prevented OP cell proliferation only if present during G1 phase; and (3) G1 blockers, such as rapamycin and deferoxamine, mimicked the anti-proliferative effects of K+ channel blockers. DFSK also prevented OP differentiation, whereas FSK hadno effect. Blockage of K+ channels and membrane depolarization also caused accumulation of the cyclin-dependent kinase inhibitors p27Kip1 and p21CIP1 in OP cells. The antiproliferative effects of K+ channel blockers and veratridine were still present in OP cells isolated from INK4a-/- mice, lacking the cyclin-dependent kinase inhibitors p16INK4a and p19ARF. Our results demonstrate that blockage of K+ channels and cell depolarization induce G1 arrest in the OP cell cycle through a mechanism that may involve p27Kip1 and p21CIP1 and further support the conclusion that OP cell cycle arrest and differentiation are two uncoupled events.

1999

20/3,AB/120 (Item 45 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12030028 BIOSIS NO.: 199900310547
Dissociation of CDK2 from cyclin A in response to the topoisomerase II inhibitor etoposide in v-src-transformed but not normal NIH 3T3 cells.
AUTHOR: Chen Guan(a); Hitomi Masahiro
AUTHOR ADDRESS: (a)Department of Molecular Biology, NC20, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Clev**USA
JOURNAL: Experimental Cell Research 249 (2):p327-336 June 15, **1999**
ISSN: 0014-4827
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Our previous work has demonstrated that treatment of NIH 3T3 cells with etoposide (VP16), an inhibitor of DNA topoisomerase II and widely used anticancer agent, results in G2/M-phase arrest, whereas treatment of cells transformed by v-src, v-ras, or v-raf results in an S-phase blockage. The present studies describe the mechanistic aspects of this selective S-phase arrest in the v-src-transformed cells. The S-phase arrest in these cells was found to be coupled with depletion of cyclin A-dependent kinase activity. This decrease could not be explained by changes in the overall level of cyclin A, CDK2, **p27**, or **p21** proteins. Rather, it was associated with a time-dependent reduction of CDK2 protein complexed with cyclin A following VP16 treatment. It was further shown that the decrease of cyclin A-associated CDK2 was linked to an increase of CDK2 protein in cyclin E immunocomplexes, which suggests that CDK2 might become redistributed following treatment with VP16. Thus, oncogenic transformation by v-src can trigger separation of CDK2 protein from cyclin A in response to VP16. This might contribute to the depletion of cyclin A-dependent kinase activity and the selective S-phase arrest by VP16 in v-src-transformed cells.

1999

20/3,AB/121 (Item 46 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12026373 BIOSIS NO.: 199900306892
1,25-Dihydroxycholecalciferol (1,25-D3) inhibits the growth of squamous cell carcinoma and down-modulates p21Waf1/Cip1 in vitro and in vivo.
AUTHOR: Hershberger Pamela A(a); Modzelewski Ruth A; Shurin Zoya R; Rueger Robert M; Trump Donald L; Johnson Candace S
AUTHOR ADDRESS: (a)Department of Pharmacology, University of Pittsburgh, W1002 Biomedical Science Tower, Pittsburgh**USA
JOURNAL: Cancer Research 59 (11):p2644-2649 June 1, **1999**
ISSN: 0008-5472
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: 1,25-Dihydroxycholecalciferol (1,25-D3) has significant antitumor effects in the murine squamous cell carcinoma (SCC) tumor model in vitro and in vivo. We investigated the basis for this antiproliferative activity and found that, in vitro, 1,25-D3 administration is associated with altered expression of cell cycle regulatory proteins, treatment results in retinoblastoma dephosphorylation, decreased expression of

p21Waf1/Cip1 (**p21**) mRNA and protein, and increased expression of p27Kip1 (**p27**) mRNA and protein. Dexamethasone, which acts synergistically with 1,25-D3 to inhibit SCC proliferation, enhanced 1,25-D3-induced down-modulation of **p21** without affecting the ability of 1,25-D3 to increase **p27** expression. 1,25-D3 did not induce cleavage of poly(ADP-ribose) polymerase. These in vitro data suggest that 1,25-D3 exerts antitumor activity in SCC by perturbing cell cycle progression rather than by inducing apoptosis. In vivo, a 1,25-D3 treatment regimen that results in a decrease in SCC tumor volume is associated with a statistically significant decrease in intratumoral **p21** expression. **p21** expression is not changed in tumors isolated from control animals or animals treated with a nontherapeutic dose of 1,25-D3. Intratumoral **p27** levels were not modulated by 1,25-D3 treatment. Thus, both in vitro and in vivo, 1,25-D3-mediated growth inhibition is associated with **p21** down-modulation.

1999

20/3,AB/122 (Item 47 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11965355 BIOSIS NO.: 199900218668
Neurotransmitter receptor activation triggers p27Kip1 and p21CIP1 accumulation and G1 cell cycle arrest in oligodendrocyte progenitors.
AUTHOR: Ghiani Cristina A; Eisen Alex M; Yuan Xiaoqing; DePinho Ronald A; McBain Chris J; Gallo Vittorio(a)
AUTHOR ADDRESS: (a)Laboratory of Cellular and Molecular Neurhysiology, NICHD, NIH, Bethesda, MD, 20892-4495**USA
JOURNAL: Development (Cambridge) 126 (5):p1077-1090 March, **1999**
ISSN: 0950-1991
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: We examined the pathways that link neurotransmitter receptor activation and cell cycle arrest in oligodendrocyte progenitors. We had previously demonstrated that glutamate receptor activation inhibits oligodendrocyte progenitor proliferation and lineage progression. Here, using purified oligodendrocyte progenitors and cerebellar slice cultures, we show that norepinephrine and the beta-adrenergic receptor agonist isoproterenol also inhibited the proliferation, but in contrast to glutamate, isoproterenol stimulated progenitor lineage progression, as determined by O4 and O1 antibody staining. This antiproliferative effect was specifically attributable to a beta-adrenoceptor-mediated increase in cyclic adenosine monophosphate, since analogs of this cyclic nucleotide mimicked the effects of isoproterenol on oligodendrocyte progenitor proliferation, while alpha-adrenoceptor agonists were ineffective. Despite the opposite effects on lineage progression, both isoproterenol and the glutamate receptor agonist kainate caused accumulation of the cyclin-dependent kinase inhibitors p27Kip1 and p21CIP1, and G1 arrest. Studies with oligodendrocyte progenitor cells from INK4a-/- mice indicated that the G1 cyclin kinase inhibitor p16INK4a as well as p19ARF were not required for agonist-stimulated proliferation arrest. Our results demonstrate that beta-adrenergic and glutamatergic receptor activation inhibit oligodendrocyte progenitor proliferation through a mechanism that may involve p27Kip1 and p21CIP1; but while neurotransmitter-induced accumulation of p27Kip1 is associated with cell cycle arrest, it does not by itself promote oligodendrocyte progenitor differentiation.

1999

20/3,AB/123 (Item 48 [redacted] file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11956870 BIOSIS NO.: 199900202979
The geranylgeranyltransferase I inhibitor GGTI-298 induces hypophosphorylation of retinoblastoma and partner switching of cyclin-dependent kinase inhibitors: A potential mechanism for GGTI-298 antitumor activity.
AUTHOR: Sun Jiazhi; Qian Yimin; Chen Zhi; Marfurt Judith; Hamilton Andrew D ; Sebti Said M(a)
AUTHOR ADDRESS: (a)Drug Discovery Program, Dept. of Biochemistry and Molecular Biology, University of South Florida**USA
JOURNAL: Journal of Biological Chemistry 274 (11):p6930-6934 March 12, **1999**
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The geranylgeranyltransferase I inhibitor GGTI-298 has recently been shown to arrest human tumor cells in the G1 phase of the cell cycle, induce apoptosis, and inhibit tumor growth in nude mice. In the present manuscript, we provide a possible mechanism by which GGTI-298 mediates its tumor growth arrest. Treatment of the human lung carcinoma cell line Calu-1 with GGTI-298 results in inhibition of the phosphorylation of retinoblastoma protein, a critical step for G1/S transition. The kinase activities of two G1/S cyclin-dependent kinases, CDK2 and CDK4, are inhibited in Calu-1 cells treated with GGTI-298. Furthermore, GGTI-298 has little effect on the expression levels of CDK2, CDK4, CDK6, cyclins D1 and E, but decreases the levels of cyclin A. GGTI-298 increases the levels of the cyclin-dependent kinase inhibitors **p21** and p15 and had little effect on those of **p27** and p16. Most interesting is the ability of GGTI-298 to induce partner switching for several CDK inhibitors. GGTI-298 promotes binding of **p21** and **p27** to CDK2 while decreasing their binding to CDK6. Reversal of partner switching and G1 block was observed after removal of GGTI-298. Furthermore, GGTI-298 treatment results in an increased binding of p15 to CDK4, which is paralleled with decreased binding to **p27**. The results demonstrate that the GGTI-298-mediated G1 block in Calu-1 cells involves increased expression and partner switching of CDK inhibitors resulting in inhibition of CDK2 and CDK4, and retinoblastoma protein phosphorylation.

1999

20/3,AB/124 (Item 49 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11949449 BIOSIS NO.: 199900195558
A new pathway for mitogen-dependent Cdk2 regulation uncovered in p27Kip1-deficient cells.
AUTHOR: Coats Steve; Whyte Peter; Fero Matthew L; Lacy Susan; Chung Grace; Randel Erin; Firpo Eduardo; Roberts James M(a)
AUTHOR ADDRESS: (a)Department of Basic Science, Fred Hutchinson Cancer Research Center, Seattle, WA**USA
JOURNAL: Current Biology 9 (4):p163-174 Feb. 25, **1999**
ISSN: 0960-9822
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background: The ability of cyclin-dependent kinases (CDKs) to promote cell proliferation is opposed by cyclin-dependent kinase inhibitors (CKIs), proteins that bind tightly to cyclin-CDK complexes and block the phosphorylation of exogenous substrates. Mice with targeted CKI gene deletions have only subtle proliferative abnormalities, however, and cells prepared from these mice seem remarkably normal when grown in vitro. One explanation may be the operation of compensatory pathways that control CDK activity and cell proliferation when normal pathways are inactivated. We have used mice lacking the CKIs **p21** Cip1 and p27Kip1 to investigate this issue, specifically with respect to CDK regulation by mitogens. Results: We show that **p27** is the major inhibitor of Cdk2 activity in mitogen-starved wild-type murine embryonic fibroblasts (MEFs). Nevertheless, inactivation of the cyclin E-Cdk2 complex in response to mitogen starvation occurs normally in MEFs that have a homozygous deletion of the **p27** gene. Moreover, CDK regulation by mitogens is also not affected by the absence of both **p27** and **p21**. A titratable Cdk2 inhibitor compensates for the absence of both CKIs, and we identify this inhibitor as p130, a protein related to the retinoblastoma gene product Rb. Thus, cyclin E-Cdk2 kinase activity cannot be inhibited by mitogen starvation of MEFs that lack both **p27** and p130. In addition, cell types that naturally express low amounts of p130, such as T lymphocytes, are completely dependent on **p27** for regulation of the cyclin E-Cdk2 complex by mitogens. Conclusions: Inhibition of Cdk2 activity in mitogen-starved fibroblasts is usually performed by the CKI **p27**, and to a minor extent by **p21**. Remarkably p130, a protein in the Rb family that is not related to either **p21** or **p27**, will directly substitute for the CKIs and restore normal CDK regulation by mitogens in cells lacking both **p27** and **p21**. This compensatory pathway may be important in settings in which CKIs are not expressed at standard levels, as is the case in many human tumors.

1999

20/3,AB/125 (Item 50 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11878889 BIOSIS NO.: 199900124998
Analysis of cell cycle arrest in adipocyte differentiation.
AUTHOR: Reichert Manuela; Eick Dirk(a)
AUTHOR ADDRESS: (a)Inst. Klin. Mol.-Biol. Tumorgenet., GSF-Forschungszentrum Umwelt Gesundheit, Marchioninistrasse **Germany
JOURNAL: Oncogene 18 (2):p459-466 Jan. 14, **1999**
ISSN: 0950-9232
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Confluent 3T3-L1 preadipocytes differentiate to adipocytes in the presence of insulin, dexamethasone, and isobutylmethylxanthine (IDI). A transient increase of DNA synthesis is induced in 3T3-L1 cells 18 h after addition of IDI, followed by an arrest in the G1 phase of the cell cycle. Growth arrested cells express the protooncogene c-myc and the gene for the CCAAT/enhancer binding protein (C/EBPalpha) between day 2 and 5. While cMyc is strongly implicated in cell proliferation, C/EBPalpha is a differentiation-specific transcription factor with antiproliferative activity. Here we have characterized the cell cycle arrest in differentiating 3T3-L1 cells. Arrested cells express the Cdk inhibitors **p21** and **p27**, but, at the same time, show hyperphosphorylation of Rb and expression of the E2F-regulated thymidine kinase gene. The addition of new serum to arrested cells resulted in cyclin A expression and Cdk2 activity, but not in DNA synthesis. Simian virus 40 large tumor antigen (LTAg) is a potent mitogen. The mutant LTAg-K1, deficient in

binding of pocket proteins and unable to induce DNA synthesis in serum-starved 3T3-L1 cells efficiently induced DNA synthesis in differentiating 3T3-L1 cells. This indicates that pocket proteins are probably not involved in the control of the cell cycle arrest during 3T3-L1 cell differentiation. Our data suggest that the differentiation specific cell cycle block in 3T3-L1 cells is resistant to high levels of c-Myc, inactivation of pocket proteins, upregulation of cyclin A levels, and Cdk2 activation, but can be abolished by a function of LTAg that is independent of binding to pocket proteins.

1999

20/3,AB/126 (Item 51 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11862517 BIOSIS NO.: 199900108626
Cell cycle profiles and expressions of p21CIP1 and p27KIP1 during myocyte development.
AUTHOR: Poolman Robert A; Gilchrist Ruth; Brooks Gavin(a)
AUTHOR ADDRESS: (a)Cardiovasc. Res. Group, Prolifix Ltd., 91 Milton Park, Abingdon, Oxon OX14 4RY**UK
JOURNAL: International Journal of Cardiology 67 (2):p133-142 Dec. 1, **1998**
ISSN: 0167-5273
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The ability of the cardiac myocyte to divide ceases shortly after birth. Thus, following severe injury, e.g., during myocardial infarction, the mature heart is unable to regenerate new tissue to replace the dead or damaged tissue. The identification of the molecules controlling the cessation of myocyte cell division may lead to therapeutic strategies which aim to re-populate the damaged myocardial area. Hence, we have determined the cell cycle profile, expressions and activities of the cyclin-dependent kinase inhibitors (CDKIs), p21CIP1 and p27KIP1, during **rat** ventricular myocyte development. Fluorescent activated cell sorting (FACS) analyses showed the percentage of S phase myocytes to be decreased significantly throughout development, concomitant with a significant increase in the percentage of G0/G1 and G2/M phase cells. The expression of p21CIP1 and p27KIP1 increased significantly throughout cardiac development and complexed differentially with a number of cyclins and CDKs. Furthermore, an adult myocyte extract reduced neonatal myocyte CDK2 kinase activity significantly (>30%, $p<0.05$) whereas immunodepletion of p21CIP1 from adult lysates restored CDK2 kinase activity. Thus, p21CIP1 and p27KIP1 may be important for the withdrawal of cardiac myocytes from the cell cycle and for maintaining the G0/G1 and G2/M phase blockades.

1998

20/3,AB/127 (Item 52 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11839845 BIOSIS NO.: 199900085954
Cyclin-dependent kinase inhibitors in restriction point control, genomic stability, and tumorigenesis.
AUTHOR: Millard S Sean(a); Koff Andrew
AUTHOR ADDRESS: (a)RRL 921, Memorial Sloan-Kettering Cancer Cent., 1275 York Avenue, New York, NY 10021**USA
JOURNAL: Journal of Cellular Biochemistry Supplement 0 (30-31):p37-42

1998
ISSN: 0733-1959
DOCUMENT TYPE: Literature Review
RECORD TYPE: Citation
LANGUAGE: English
1998

20/3,AB/128 (Item 53 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11814013 BIOSIS NO.: 199900060122
Inactivation of the cyclin-dependent kinase inhibitor **p27** upon loss of the tuberous sclerosis complex gene-2.
AUTHOR: Soucek Thomas; Yeung Raymond S; Hengstschlaeger Markus(a)
AUTHOR ADDRESS: (a)Obstet. Gynecol., Univ. Vienna, Dep. Prenatal Diagn. Therapy, Wahringer Gurtel 18-20, A-1090 Vie**Austria
JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 95 (26):p15653-15658 Dec. 22, **1998**
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Tuberous sclerosis is an autosomal dominant disorder characterized by the development of aberrant growths in many tissues and organs. Linkage analysis revealed two disease-determining genes on chromosome 9 and chromosome 16. The tuberous sclerosis complex gene-2 (TSC2) on chromosome 16 encodes the tumor suppressor protein tuberin. We have shown earlier that loss of TSC2 is sufficient to induce quiescent cells to enter the cell cycle. Here we show that TSC2-negative fibroblasts exhibit a shortened G1 phase. Although the expression of cyclin E, cyclin A, **p21**, or Cdc25A is unaffected, TSC2-negative cells express much lower amounts of the cyclin-dependent kinase (CDK) inhibitor **p27** because of decreased protein stability. In TSC2 mutant cells the amount of **p27** bound to CDK2 is diminished, accompanied with elevated kinase activity. Ectopic expression studies revealed that the aforementioned effects can be reverted by transfecting TSC2 in TSC2-negative cells. High ectopic levels of **p27** have cell cycle inhibitory effects in TSC2-positive cells but not in TSC2-negative counterparts, although the latter still depend on CDK2 activity. Loss of TSC2 induces soft agar growth of fibroblasts, a process that cannot be inhibited by high levels of **p27**. Both phenotypes of TSC2-negative cells, their resistance to the activity of ectopic **p27**, and the instability of endogenous **p27**, could be explained by our observation that the nucleoprotein **p27** is mislocated into the cytoplasm upon loss of TSC2. These findings provide insights into the molecular mechanism of how loss of TSC2 induces cell cycle entry and allow a better understanding of its tumor suppressor function.

1998

20/3,AB/129 (Item 54 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11773477 BIOSIS NO.: 199900019586
Glucocorticoids stimulate P21CIP1 gene population activity and inhibit mesangial cell cycle: Involvement of C/EBPalpha in transcription of P21CIP1.
AUTHOR: Okado Tomokazu; Terada Yoshio; Inoshita Seiji; Nakashima Osamu; Kuwahara Michio; Sasaki Sei; Marumo Fumiaki
AUTHOR ADDRESS: Tokyo Medical Dental Univ., Tokyo**Japan

JOURNAL: Journal of the American Society of Nephrology 9 (PROGRAM AND ABSTR. ISSUE):p444A Sept., [redacted]
CONFERENCE/MEETING: 31st Annual Meeting of the American Society of Nephrology Philadelphia, Pennsylvania, USA October 25-28, 1998
SPONSOR: American Society of Nephrology
ISSN: 1046-6673
RECORD TYPE: Citation
LANGUAGE: English
1998

20/3,AB/130 (Item 55 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11770128 BIOSIS NO.: 199900016237
Activation of neurotransmitter receptors regulates cell cycle progression and differentiation of oligodendrocyte progenitors.
AUTHOR: Ghiani C A; Eisen A M; Yuan X; McBain C J; Gallo V
AUTHOR ADDRESS: Lab. Cell. and Mol. Neurophysiol., NICHD, NIH, Bethesda, MD 20892-4495**USA
JOURNAL: Molecular Biology of the Cell 9 (SUPPL.):p369A Nov., **1998**
CONFERENCE/MEETING: 38th Annual Meeting of the American Society for Cell Biology San Francisco, California, USA December 12-16, 1998
SPONSOR: American Society for Cell Biology
ISSN: 1059-1524
RECORD TYPE: Citation
LANGUAGE: English
1998

20/3,AB/131 (Item 56 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11767522 BIOSIS NO.: 199900013631
Differential modulation of cell-cycle regulatory proteins in **rat** vascular smooth muscle cells (VSMC) by trapidil and cAMP.
AUTHOR: Ishikura Kenji; Hida Mariko; Hoshiya Makiko; Awazu Midori
AUTHOR ADDRESS: Dep. Pediatr., Keio Univ. Sch. Med., Tokyo**Japan
JOURNAL: Journal of the American Society of Nephrology 9 (PROGRAM AND ABSTR. ISSUE):p425A Sept., **1998**
CONFERENCE/MEETING: 31st Annual Meeting of the American Society of Nephrology Philadelphia, Pennsylvania, USA October 25-28, 1998
SPONSOR: American Society of Nephrology
ISSN: 1046-6673
RECORD TYPE: Citation
LANGUAGE: English
1998

20/3,AB/132 (Item 57 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11762610 BIOSIS NO.: 199900008719
The differential role of cyclin kinase inhibitors (CKI) in unilateral ureteral obstruction (UUO).
AUTHOR: Hughes J; Shankland S J
AUTHOR ADDRESS: Univ. Washington, Seattle, WA**USA
JOURNAL: Journal of the American Society of Nephrology 9 (PROGRAM AND ABSTR. ISSUE):p440A-441A Sept., **1998**
CONFERENCE/MEETING: 31st Annual Meeting of the American Society of Nephrology Philadelphia, Pennsylvania, USA October 25-28, 1998
SPONSOR: American Society of Nephrology

ISSN: 1046-6673
RECORD TYPE: Citation
LANGUAGE: English
1998

20/3,AB/133 (Item 58 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11760782 BIOSIS NO.: 199900006891
Investigation of the cell cycle regulation of cdk3-associated kinase activity and the role of cdk3 in proliferation and transformation.
AUTHOR: Braun Katja; Hoezl Gabriele; Soucek Thomas; Geisen Christoph; Moereoy Tarik; Hengstschlaeger Markus(a)
AUTHOR ADDRESS: (a)Obstet. Gynecol., Univ. Vienna, Dep. Prenatal Diagn. Ther., Waehringer Guertel 18-20, A-1090 Vie**Austria
JOURNAL: Oncogene 17 (17):p2259-2269 Oct. 29, **1998**
ISSN: 0950-9232
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The G1-S transition in mammalian cells has been demonstrated to require the cyclin-dependent kinases cdk2, cdk3 and cdk4/6. Here we show that a novel kinase activity associated with cdk3 fluctuates throughout the cell cycle differently from the expression of cyclin D1-, E- and A-associated kinase activities. Cdk3 kinase activity is neither affected by p16 (in contrast to cdk4/6) nor by E2F-1 (in contrast to cdk2), but is downregulated upon transient **p27** expression. We found cdk3 to bind to **p21** and **p27**. We provide evidence that **p27** could be involved in the regulation of the cell cycle fluctuation of cdk3 activity: cdk3 protein does not fluctuate and interaction of cdk3 with **p27**, but not with **p21**, is lost when cdk3 kinase becomes active during the cell cycle. In Myc-overexpressing cells, but not in normal Rat1 cells, constitutive ectopic expression of cdk3 induces specific upregulation of cdk3-associated kinase activity that is still cell cycle phase dependent. Ectopic cdk3, but not cdk2, enhances Myc-induced proliferation and anchorage-independent growth associated with Myc activation, without effects on cyclin D1, E and A protein expression or kinase activities. High levels of cdk3 in Mycoverexpressing cells trigger up- and deregulation of E2F-dependent transcription without inducing the E2FDNA binding capacity. In contrast to all other studied positive G1 regulators, cdk3 is unable to cooperate with ras in fibroblast transformation suggesting a function of cdk3 in G1 progression that is different from cyclin Dor E-associated kinase activities. Our data provide first insights into the regulation of cdk3-associated kinase activity and suggest a model how cdk3 participates in the regulation of the G1-S transition.

1998

20/3,AB/134 (Item 59 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11700349 BIOSIS NO.: 199800482080
Hormone-induced refractoriness to mammary carcinogenesis in Wistar-Furth rats.
AUTHOR: Sivaraman Lakshmi; Stephens L Clifton; Markaverich Barry M; Clark James A; Krnacik Susanne; Conneely Orla M; O'Malley Bert W; Medina Daniel (a)
AUTHOR ADDRESS: (a)Dep. Cell Biol., Baylor Coll. Med., Houston, TX 77030** USA

JOURNAL: Carcinogenesis (Oxford) 19 (9):p1573-1581 Sept., 1998
ISSN: 0143-3334
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: One of the most consistent results in the epidemiology of human breast cancer is the inverse relationship of risk and early full-term parity. The goal of this study was to investigate the molecular mechanisms through which early full-term pregnancy protects the breast from cancer development. We used Wistar-Furth (WF) rats as our experimental system and mimicked pregnancy using estrogen and progesterone (E/P). Sexually mature female rats were treated with steroid hormones for 21 days and after 28 days of gland involution, the rats were administered MNU. Rats that received a high dose of 20 mug E and 20 mg P exhibited an 82% reduction in the incidence of mammary adenocarcinomas as compared to the rats receiving only blank pellets. Decreasing doses of E/P were partially protective suggesting that complete differentiation of the gland was not required for refractoriness. We measured the RNA expression levels of several target genes involved in the regulation of mammary cell proliferation and/or differentiation including estrogen receptor (ER) and progesterone receptor (PR), cyclins D1 and D2, the cell cycle inhibitors p16, **p21** and **p27**, and the tumor suppressor p53. At the time of MNU treatment we found no significant differences in the expression of these genes, with the possible exception of **p21**, indicating that hormone treatment did not result in constitutive changes in expression levels. The numbers of apoptotic cells were low and comparable in the hormone exposed and age-matched virgin gland (AMV) at the time of carcinogen challenge and remained low for 8 days after MNU treatment. The number of BrdU-labeled cells at the time of carcinogen challenge were also low in both the AMV (1.8%) and hormone exposed (0.8%) animals. In contrast, cell proliferation in the AMV (5.7%) was significantly different from both the parous involuted (1.2%) and the E/P-treated involuted (1.5%) animals 8 days after MNU treatment. We interpret these data to indicate that hormone treatment results in mammary epithelial cells that have persistent alterations in intracellular pathways governing proliferation responses to carcinogens.

1998

20/3,AB/135 (Item 60 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11678170 BIOSIS NO.: 199800459901
Adenoviral iNOS gene transfer inhibits smooth muscle cell proliferation through the upregulation of **P27**.
AUTHOR: Kibbe M R; Billiar T R; Tzeng E
AUTHOR ADDRESS: Dep. Surg., Univ. Pittsburgh, Pittsburgh, PA**USA
JOURNAL: Nitric Oxide 2 (2):p80 **1998**
CONFERENCE/MEETING: Third International Conference on Biochemistry and Molecular Biology of Nitric Oxide Los Angeles, California, USA July 11-15, 1998
SPONSOR: Nitric Oxide Society
ISSN: 1089-8603
RECORD TYPE: Citation
LANGUAGE: English
1998

20/3,AB/136 (Item 61 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11669070 BIOSIS NO.: 199800450801
Time course of cell cycle-related protein expression in diethylnitrosamine-initiated **rat** liver.
AUTHOR: Lee Yun-Sil; Kim Woo-Ho; Yu Eun Sil; Kim Mee-Rhan; Lee Min-Jae; Jang Ja-June(a)
AUTHOR ADDRESS: (a)Dep. Pathol., Seoul Natl. Univ. Coll. Med., 28 Yongon-dong, Chongro-gu, Seoul 110-799**South Korea
JOURNAL: Journal of Hepatology 29 (3):p464-469 Sept., **1998**
ISSN: 0168-8278
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background/Aims: Cell cycle control and the relationship that exists between cellular proliferation, the expression of cell cycle control proteins and cancer have been reported. This study was designed to decipher the timing of cell cycle control protein expression during the initiation of diethylnitrosamine-induced **rat** hepatocarcinogenesis. Methods: Three-week-old female Sprague-Dawley rats were intraperitoneally injected twice in 1 week with diethylnitrosamine; after the second injection, all animals were sacrificed at 1, 2 and 24 h, and 3 and 7 days. The expression of cell cycle-related proteins such as CDK2 and 4, cyclin proteins (D1, E and cdc2), proliferating cell nuclear antigen, tumor suppressor proteins (p53 and Rb), CDK inhibitory proteins (p21Waf1 and p27Kip1), and apoptosis-inhibiting protein (bcl-2) following diethylnitrosamine treatment was examined. Results: The peak induction time of each cell cycle-related protein during DEN-induced cellular proliferation was diverse, and expressions of CDK2, CDK4, cdc2, p53, bcl-2, p21Waf1 and p27Kip1 appear to be of the greatest interest. Conclusions: Data generated from this study may provide information about cell cycle-related protein expression in the initiation stage of hepatocarcinogenic signaling pathways stimulated by a genotoxic agent such as diethylnitrosamine.

1998

20/3,AB/137 (Item 62 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11654234 BIOSIS NO.: 199800435965
Molecular characterisation of a panel of human ovarian carcinoma xenografts.
AUTHOR: Codegoni A M(a); Nicoletti M I; Buraggi G; Valoti G; Giavazzi R; D'Incalci M; Landoni F; Maneo A; Broggini M
AUTHOR ADDRESS: (a)Mario Negri Inst. Pharmacol. Res., via Eritrea 62, 20157 Milan**Italy
JOURNAL: European Journal of Cancer 34 (9):p1432-1438 Aug., **1998**
ISSN: 0959-8049
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In a panel of 16 human ovarian tumours transplanted in nude mice, the expression of genes involved in cell cycle regulation and in response to drug treatment were characterized. In the 16 tumours analysed we could not detect overexpression of Erb-B2 oncogene while expression of MDR1 mRNA was not detected in 11/15 samples and was low in 4/15 tumours. Only three tumours had mutations in the p.53 gene exons 5-8 and one of these mutations did not result in any amino acid alteration. The levels of mRNA for cyclins A, D1 and E were heterogeneous with some tumours expressing high levels and others not expressing them at all. The same was found for the cyclin dependent kinases (CDK) CDK2 and CDK4 and for CDK inhibitors **p21**/WAF1, **p27**/KIP1 and p16/CDKN2. Two genes

belonging to the nucleotide excision repair, ERCC1 and ERCC2 were detectable in all the samples examined, as were the genes [redacted]T and MAG, also involved in DNA repair. The data indicate a heterogeneity in the expression of genes considered to be involved in the cellular responses to cytotoxic drug treatment and indicate the possibility of using these tumour models to test specifically molecules with a defined mechanism of action.

1998

20/3,AB/138 (Item 63 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11575869 BIOSIS NO.: 199800356565
Blockade of TGFbeta3 up-regulation of p27Kip1 and p21Cip1 by expression of RasN17 in epithelial cells.
AUTHOR: Yue Jianbo; Buard Annie; Mulder Kathleen M(a)
AUTHOR ADDRESS: (a)Dep. Pharmacol., Pennsylvania State Univ. Coll. Med., Hershey, PA 17033**USA
JOURNAL: Oncogene 17 (1):p47-55 July 9, **1998**
ISSN: 0950-9232
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Our previous data demonstrated that Ras activation is necessary and sufficient for transforming growth factor beta (TGFbeta)-mediated Erk1 activation, and is partially required for the inhibition of cyclin-dependent kinase 2 (Cdk2) activity, cyclin A expression and DNA synthesis by TGFbeta (KM Mulder and SL Morris, J. Biol. Chem., 267: 5029-5031, 1992; MT Hartsough and KM Mulder, J. Biol. Chem., 270: 7117-7124, 1995; and MT Hartsbourgh et al., J. Biol. Chem., 271: 22368-22375, 1996). Here, we examined the kinetics and role of RAS in TGFbeta3-mediated effects on specific G1 cell cycle components in TGFbeta-sensitive (4-1) and TGFbeta-resistant (4-6) intestinal epithelial cells (IEC's). Our results indicate that inactivation of Ras by stable, inducible expression of a dominant-negative mutant of Ras (RasN17) completely abrogated the ability of TGFbeta3 to up-regulate both CKI's. In contrast, the ability of TGFbeta3 to up-regulate p27Kip1 and p21Cip1 was maintained in ZnCl2-treated control cells. Inactivation of Ras also completely blocked the rapid TGFbeta-mediated increase in new synthesis of p27Kip1 protein. Moreover, up-regulation of p21Cip1 protein levels and new synthesis of p27Kip1, as well as the association of these CKI's with Cdk2, preceded the decrease in Cdk2 activity by TGFbeta. Collectively, our results suggest that p21Cip1 and p27Kip1 are upstream effectors of the TGFbeta-mediated inhibition of Cdk2 activity in IEC 4-1 cells, and demonstrate that Ras activation is obligatory for TGFbeta-mediated upregulation of these CKIs in untransformed epithelial cells.

1998

20/3,AB/139 (Item 64 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11524156 BIOSIS NO.: 199800305488
Cytoplasmic displacement of cyclin E-cdk2 inhibitors **p21**!C!i!p!1 and **p27**!K!i!p!1 in anchorage-independent cells.
AUTHOR: Orend G; Hunter T; Ruoslahti E(a)
AUTHOR ADDRESS: (a)La Jolla Cancer Res. Cent., Burnham Inst., La Jolla, CA 92037**USA
JOURNAL: Oncogene 16 (20):p2575-2583 May 21, **1998**

ISSN: 0950-9232
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Loss of attachment to an extracellular matrix substrate arrests the growth of untransformed cells in the GI phase. This anchorage-dependent cell cycle arrest is linked to increased expression of the **p21**!C!i!p!1 (**p21**) and **p27**!K!i!p!1 (**p27**) cyclin-dependent kinase inhibitors. The result is a loss of cdk2-associated kinase activity, especially that of cyclin E-cdk2. The levels of **p21** and **p27** are also upregulated in unattached transformed cells, but cyclin E-cdk2 activity remains high, and the cells are able to grow in an anchorage-independent manner. Increased expression of cyclin E and cdk2 appears to be partially responsible for the maintenance of cyclin E-cdk2 activity in transformed cells. To explore further the regulation of cyclin E-cdk2 in transformed cells, we have analysed the subcellular distribution of cyclin-cdk complexes and their inhibitors in normal human fibroblasts, their transformed counterparts, and in various human tumor cell lines. In substrate-attached normal fibroblasts, cyclin E and cdk2 were exclusively in the nuclear fraction, associated with one another. When normal fibroblasts were detached and held in suspension, cyclin E-cdk2 complexes remained nuclear, but were now found associated with the **p21** and **p27** cdk inhibitors and lacked histone H1 phosphorylating activity. In contrast, the transformed fibroblasts and tumor cells, which are anchorage-independent, had more than half of their cyclin E, cdk2, **p21** and **p27** in the cytoplasmic fraction, both in attached and suspended cultures. The cytoplasmic **p21** and **p27** were bound to cyclin E-cdk2, as well as to complexes containing cyclin A and cyclin D. The nuclear cyclin E-cdk2 complexes from the transformed cells grown in suspension contained only low levels of **p21** and **p27** and had histone H1 kinase activity. Thus, at least three mechanisms contribute to keeping cyclin E-cdk2 complexes active in suspended anchorage-independent cells: cyclin E and cdk2 are upregulated, as reported previously, cdk inhibitors are sequestered away from the nucleus by cytoplasmic cyclin-cdk complexes, and the binding of the inhibitors to nuclear cyclin E-cdk2 complexes is impaired.

1998

20/3,AB/140 (Item 65 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11512955 BIOSIS NO.: 199800294287
1,25D|3 dihydroxyvitamin D|3 (1,25D|3) as an anti-cancer agent for prostate cancer: Preclinical studies.
AUTHOR: Johnson Candace S; Hershberger Pamela A; Modzelewski Ruth A; Trump Donald L
AUTHOR ADDRESS: Pittsburgh, PA**USA
JOURNAL: Journal of Urology 159 (5 SUPPL.):p11 May, **1998**
CONFERENCE/MEETING: 93rd Annual Meeting of the American Urological Association, Inc. San Diego, California, USA May 30-June 4, 1998
SPONSOR: American Urological Association
ISSN: 0022-5347
RECORD TYPE: Citation
LANGUAGE: English
1998

20/3,AB/141 (Item 66 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11510662 BIOSIS NO.: 1998[redacted]91994
Release of melanocytes from external growth inhibitory signals by overexpressed mutant transcription factor E2F1|E|1|3|2, but not by disruption of p16!I!N!K!4!A, **p21**!W!A!F!1!/!C!I!P!1 or **p27** !K!I!P!1 genes.
AUTHOR: Halaban Ruth; Cheng Elaine; Zhang Yuhau; Mandigo Christopher; Miglarese Mark R
AUTHOR ADDRESS: Dep. Dermatol., Yale Univ. Sch. Med., New Haven, CT**USA
JOURNAL: Journal of Dermatological Science 16 (SUPPL. 1):pS6 March, **1998**
CONFERENCE/MEETING: Third Joint Meeting of the European Society for Dermatological Research, Japanese Society for Investigative Dermatology, Society for Investigative Dermatology Cologne, Germany May 7-10, 1998
SPONSOR: European Society for Dermatological Research
ISSN: 0923-1811
RECORD TYPE: Citation
LANGUAGE: English
1998

20/3,AB/142 (Item 67 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11502117 BIOSIS NO.: 199800283449
Molecular bases of X induced cell cycle arrest and apoptosis.
AUTHOR: Sirma H; Giannini C; Kremsdorf D; Brechot C
AUTHOR ADDRESS: INSERM U370, Inst. Necker, Paris**France
JOURNAL: Journal of Hepatology 28 (SUPPL. 1):p87 **1998**
CONFERENCE/MEETING: 33rd Annual Meeting of the European Association for the Study of the Liver Lisbon, Portugal April 15-18, 1998
SPONSOR: European Association for the Study of the Liver
ISSN: 0168-8278
RECORD TYPE: Citation
LANGUAGE: English
1998

20/3,AB/143 (Item 68 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11472411 BIOSIS NO.: 199800253743
Involvement of **p21** and **p27** in the regulation of CDK activity and cell cycle progression in the regenerating liver.
AUTHOR: Albrecht Jeffrey H(a); Poon Randy Y C; Ahonen Cory L; Rieland Brenda M; Deng Chuxia; Crary Gretchen S
AUTHOR ADDRESS: (a)Dep. Med., Hennepin County Med. Cent., 701 Park Avenue, Minneapolis, MN 55415**USA
JOURNAL: Oncogene 16 (16):p2141-2150 April 23, **1998**
ISSN: 0950-9232
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In tissue culture systems, **p21** and **p27** inhibit cyclin-dependent kinase (CDK) activity and cell cycle progression in response to numerous stimuli, but little is known about their involvement in cell growth in vivo. We examined the modulation of CDK activity by these proteins after 70% partial hepatectomy (PR), an in vivo model of synchronous hepatocyte cell cycle progression. After PR in BALB/c mice, **p21** was induced during the prereplicative (G1) phase and was maximally expressed after peak hepatocyte DNA synthesis. **p27** was present in quiescent liver and was minimally induced after PR. **p21**

and **p27** immunoprecipitated with CDK2, CDK4, and cyclin D1 in the regenerating liver. The activity of CDK2-, CDK4- and cyclin D1-associated kinases was upregulated after PR, and maximal activity of these enzyme complexes corresponded to peak DNA synthesis. Immunodepletion experiments suggested that **p27** plays a role in downregulating CDK2 activity before and after peak DNA synthesis. Compared to cogenic wild-type mice, **p21**-/- mice demonstrated evidence of markedly accelerated hepatocyte progression through G1 phase after PR: DNA synthesis, upregulation of cyclin A and PCNA, induction of cyclin D1- and CDK2-associated kinase activity, and appearance of a phosphorylated retinoblastoma protein (Rb) species occurred earlier in the **p21**-/- mice. These results suggest that **p21** and **p27** modulate CDK activity in the regenerating liver, and that **p21** regulates the rate of progression through GI phase of the cell cycle in vivo.

1998

20/3,AB/144 (Item 69 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11466056 BIOSIS NO.: 199800247388
Release of melanocytes from external growth inhibitory signals by overexpressed mutant transcription factor E2F1|E|1|3|2, but not by disruption of p16!I!N!K!4!A, **p21**!W!A!F!/!C!I!P!1 or **p27** !K!I!P!1 genes.
AUTHOR: Halaban Ruth; Cheng Elaine; Zhang Yuhau; Mandigo Christopher; Miglarese Mark R
AUTHOR ADDRESS: Dep. Dermatol., Yale Univ. Sch. Med., New Haven, CT**USA
JOURNAL: Journal of Investigative Dermatology 110 (4):p478 April, **1998**
CONFERENCE/MEETING: Annual Meeting of the International Investigative Dermatology Cologne, Germany May 7-10, 1998
SPONSOR: The Society for Investigative Dermatology, Inc.
ISSN: 0022-202X
RECORD TYPE: Citation
LANGUAGE: English
1998

20/3,AB/145 (Item 70 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11449781 BIOSIS NO.: 199800231113
Cell cycle-related gene expression in the adult **rat** brain: Selective induction of cyclin G1 and **p21**!W!A!F!1!/!C!I!P!1 in neurons following focal cerebral ischemia.
AUTHOR: van Lookeren Campagne M; Gill R(a)
AUTHOR ADDRESS: (a)Hoffmann-La Roche Ltd., PRPN, Bau 68,410, Grenzacherstrasse 124, CH-4070 Basel**Switzerland
JOURNAL: Neuroscience 84 (4):p1097-1112 June, **1998**
ISSN: 0306-4522
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The present studies were initiated to investigate whether p53 transactivated target genes are induced in a **rat** model of focal cerebral ischemia. Therefore, we applied in situ hybridization, immunocytochemistry and western blotting to study the temporal and spatial expression of p53 and its transcriptional targets Bax, **p21** and cyclin G1 following permanent middle cerebral artery occlusion in the **rat**. Cyclin G1 immunoreactivity was constitutively expressed in the

nuclei of cells in the choroid plexus and ependymal cell layer and in the cytoplasm of cell bodies and dendrites of pyramidal neurons of the cerebral cortex. Cyclin G1 messenger RNA and protein levels transiently increased to 150% of contralateral levels in neurons of the ipsilateral frontal and parietal cortex and striatum 3 h following middle cerebral artery occlusion. A low level of constitutively expressed **p21** messenger RNA and protein was found in nuclei of cells in the choroid plexus, oligodendrocytes and neurons. **p21** messenger RNA and protein levels gradually increased to 250% and 140% of contralateral levels in areas bordering the infarct core up to 6 h following middle cerebral artery occlusion. In contrast, p53 and Bax messenger RNA and protein levels, and protein levels of **p27**, cyclin-dependent kinase 5, p35 and cyclin E decreased in the infarct core and border areas with time after middle cerebral artery occlusion. The selective up-regulation of cyclin G1 and **p21** in neurons in the border zone of a focal ischemic infarct indicates their involvement in an adaptive response to ischemic injury. The possible participation of cyclin G1 and **p21** in a signal transduction pathway associated with ischemia-induced cellular stress is discussed.

1998

20/3,AB/146 (Item 71 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11433972 BIOSIS NO.: 199800215304
BDNF accelerates gene expression in cultured cerebellar granule neurons.
AUTHOR: Lin Xi; Cui Hong; Bulleit Robert F(a)
AUTHOR ADDRESS: (a)Dep. Pharmacol., Univ. Maryland Sch. Med., 655 W. Baltimore St., RM 4-018 Baltimore, MD 21201**USA
JOURNAL: Developmental Brain Research 105 (2):p277-286 Feb. 10, **1998**
ISSN: 0165-3806
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: This study reports that in purified cultures of postnatal cerebellar granule cells, BDNF significantly accelerated GABAA receptor alpha6 subunit (GABAAalpha6) mRNA expression, a marker for terminally differentiated cerebellar granule neurons, and also accelerated p21cip1 expression. p21cip1 is a general cyclin-dependent kinase (Cdk) inhibitor that can inhibit progression through the cell cycle. Alternatively, the expression of p27kip1, another Cdk inhibitor closely related to p21cip1, is not modified by BDNF. In cultured granule cells, the increase in p21cip1 expression induced by BDNF occurred after dividing granule cells had left the cell cycle and thus was not required to direct granule neuron precursors out of the cell cycle. p21cip1 may have an alternative function during granule neuron terminal differentiation, separate from its ability to regulate cell cycle exit. This report shows that, in vitro, BDNF accelerates granule cell gene expression and may thus modulate cerebellar granule cell differentiation.

1998

20/3,AB/147 (Item 72 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11426091 BIOSIS NO.: 199800207423
Changes in E2F complexes containing retinoblastoma protein family members and increased cyclin-dependent kinase inhibitor activities during terminal differentiation of cardiomyocytes.

AUTHOR: Flink Irwin L(a); Oana Shinji; Maitra Niranjan; Bahl Joseph J; Morkin Eugene
AUTHOR ADDRESS: (a)Univ. Heart Center, Dep. Med., Univ. Arizona, Tucson, AZ 85724**USA
JOURNAL: Journal of Molecular and Cellular Cardiology 30 (3):p563-578 March, **1998**
ISSN: 0022-2828
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Cardiomyocyte terminal differentiation was examined by studying the interaction of retinoblastoma protein (pRb) family members with E2F during the developmental transition from 17-day fetal to 2-day neonatal. Additionally, the expression pattern of cyclins, cyclin-dependent kinases (CDKs), and CDK inhibitors responsible for modulating the phosphorylation of pRb were studied. p107, pRb, and p130 are regulators of cellular proliferation, differentiation, and cell cycle exit and entry, respectively. The active, underphosphorylated form of these proteins targets the E2F family of transcriptional factors that play a critical role in the control of genes associated with DNA synthesis. Electromobility shift analyses demonstrated E2F complexed with p107 in proliferating fetal cardiomyocytes, whereas in 2-day neonatal cells, E2F was principally associated with p130 and a low level of pRb. At the 2-day neonatal stage, decreased protein levels were observed for cyclins D|2, D|3, and E, and CDK2 and CDK4. No changes were observed in the mRNA levels of the D-cyclins in neonatal cells; however, the transcripts for cyclins A and E and CDK4 were diminished. In skeletal myoblasts, differentiation is associated with induction of **p21**, a CDK inhibitor, by a MyoD-dependent pathway. Although heart cells lack MyoD, CDK assays demonstrated that the activity of CDKs 2, 4, and 6 were downregulated in 2-day neonatal cells, and CDC2 was increased. RT-PCR indicated that **p21** mRNA was induced 1.4-, 2.0-, and 3.1-fold in the 2-day neonatal, 7-day neonatal, and adult stages, respectively, compared to the 17-day fetal stage. At the protein level, **p21** also increased at the 2-day neonatal stage. Kinase inhibitory immunodepletion assays showed that CDK inhibitory activity was markedly increased in the 2-day neonate. Although mRNA levels of the **p27** CDK inhibitor were unchanged, its protein level and inhibitory effect on CDK2 and CDK4 were increased. Thus, cardiomyocytes retain the capacity to proliferate until the early neonatal period when a series of changes occur, including a switch in pRb partners, a decrease in CDK levels and induction of CDK inhibitory activity, which is associated with terminal differentiation.

1998

20/3,AB/148 (Item 73 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11426084 BIOSIS NO.: 199800207416
Persistent and heterogenous expression of the cyclin-dependent kinase inhibitor, **p27**!K!I!P!1, in **rat** hearts during development.
AUTHOR: Koh Keum Nim; Kang Min Jeong; Frith-Terhune Amy; Park Sung Kwang; Kim Injune; Lee Chin Ok; Koh Gou Young(a)
AUTHOR ADDRESS: (a)Dep. Physiol. and Inst. Cardiovascular Res., Chonbuk National Univ. Sch. Med., San 2-20, Keum-Am**South Korea
JOURNAL: Journal of Molecular and Cellular Cardiology 30 (3):p463-474 March, **1998**
ISSN: 0022-2828
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We have previously shown that there were differential and dramatic decreases of cyc[redacted] and cyclin-dependent kinase [redacted]) activities in cardiomyocytes during the neonatal period. The activity of CDKs control cell cycle progression, and this activity is regulated positively and negatively by association of CDKs with cyclins and cyclin-dependent kinase inhibitors (CKIs), respectively. White the INK family (p!1!5!I!N!K!4!B/p16!I!N!K!4!A/p18!I!N!K!4!C/p19!I!N!K!4!D) of CKIs is not detectable in hearts, the KIP/CIP family (**p21**!C!I!P!1, **p27**!K!I!P!1 and p57!K!I!P!2) of CKIs is detectable in most organs including the heart. Differential and dramatic changes of the KIP/CIP family (**p21**!C!I!P!1, **p27**!K!I!P!1 and p57!K!I!P!2) of CKIs were detected in **rat** hearts during development. The mRNA and protein levels of **p21**!C!I!P!1 and p57!K!I!P!2 were readily detectable in hearts at gestational and early postnatal periods and decreased thereafter. The mRNA levels of **p27**!K!I!P!1 in ventricles were high during the gestational period, and did not change until day 30 postnatal, then were decreased slightly in 90-day-old rats. The protein levels of **p27**!K!I!P!1 increased significantly in the early postnatal period, then were expressed persistently, although levels decreased slightly in the adult period. However, protein levels of **p27**!K!I!P!1 in atria did not change during development. Variable immuno-staining patterns of **p27**!K!I!P!1 were observed at different periods of development and in various locations in myocardium. During the gestational period, approximately 35-50% of myocardial cells in the cardiac wall were **p27**!K!I!P!1 immunopositive and were distributed diffusely. These **p27**!K!I!P!1 immunopositive cells increased predominantly in endocardial and mid-portion areas of ventricular myocardium at the early postnatal period. This heterogenous pattern of **p27**!K!I!P!1 protein expression persisted to adult hearts though the percentage of **p27**!K!I!P!1 immunopositive cells decreased slightly. High magnification revealed that more than 50% of adult cardiomyocytes were **p27**!K!I!P!1 immunopositive and that **p27**!K!I!P!1 was located solely in nuclei. These results indicate that **p27**!K!I!P!1 may be an important inhibitor of CDK activities in cardiomyocytes during early postnatal development and may block the re-entrance of adult cardiomyocytes into the cell cycle after injury.

1998

20/3,AB/149 (Item 74 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11414681 BIOSIS NO.: 199800196013
1,25-Dihydroxycholecalciferol (1,25-D|3) induces G|0/G|1 arrest and modulates expression of **p21**!W!A!F!1/|C|i|p!1 and **p27**|K|i|p|1 in solid tumors.
AUTHOR: Hershberger P A(a); Modzelewski A; Trump D L; Johnson C S
AUTHOR ADDRESS: (a)Dep. Pharmacol., Univ. Pittsburgh, Pittsburgh, PA 15213 **USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 39p313 March, **1998**
CONFERENCE/MEETING: 89th Annual Meeting of the American Association for Cancer Research New Orleans, Louisiana, USA March 28-April 1, 1998
SPONSOR: American Association for Cancer Research
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
1998

20/3,AB/150 (Item 75 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11412635 BIOSIS NO.: 1998[illegible]93967
Expression of **p21** and **p27** during castration induced regression of prostatic adenocarcinoma.
AUTHOR: Myers R B(a); Oelschlager D K; Pretlow T; Coan P N; Grizzle W E
AUTHOR ADDRESS: (a)Dep. Pathol., Univ. Alabama at Birmingham, Birmingham, AL 35294**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 39p14 March, **1998**
CONFERENCE/MEETING: 89th Annual Meeting of the American Association for Cancer Research New Orleans, Louisiana, USA March 28-April 1, 1998
SPONSOR: American Association for Cancer Research
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
1998

20/3,AB/151 (Item 76 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11341778 BIOSIS NO.: 199800123110
p27!K!i!p!1 is expressed transiently in developing myotomes and enhances myogenesis.
AUTHOR: Zabludoff Sonya D; Csete Marie; Wagner Roger; Yu Xin; Wold Barbara J(a)
AUTHOR ADDRESS: (a)Division Biol., 156-29 California Inst. Technol., Pasadena, CA 91125**USA
JOURNAL: Cell Growth & Differentiation 9 (1):p1-11 Jan., **1998**
ISSN: 1044-9523
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Vertebrate skeletal muscle development is characterized by tight coupling of muscle differentiation with cell cycle arrest in G|1/G|0. Key regulators of G|1 progression are the G|1 cyclin-dependent kinases, their positive regulators, the G|1 cyclins, and their negative regulators, the cyclindependent kinase inhibitors (CDIs). Here we show that **p27** !K!i!p!1 protein, a G|1 CDI, is expressed in a prominent but transient wave in the developing myotomes of the **mouse** embryo. We relate its expression to expression of MyoD and myogenin proteins, which are determination and differentiation class myogenic regulatory factors, respectively. Functional assays showed that ectopic **p27** expression can powerfully enhance the efficiency of MyoD-initiated muscle differentiation in cell culture. When considered together with the myotomal expression patterns of p18, **p21** and p57, these results suggest a model in which **p27** acts as a "trigger" CDI while myoblasts are exiting the cell cycle and initiating differentiation. At later times, when **p27** protein has been down-regulated, it is proposed that accumulation of p18, **p21**, and p57 maintain the differentiated myocytes in a postmitotic state.

1998

20/3,AB/152 (Item 77 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11315889 BIOSIS NO.: 199800097221
Functional development of intrinsic properties in ganglion cells of the mammalian retina.
AUTHOR: Wang Guo-Yong; Ratto G-M; Bisti Silvia; Chalupa Leo M(a)

AUTHOR ADDRESS: (a)Cent. Neurosci., Univ. Calif., Davis, CA 95616**USA
JOURNAL: Journal of Neurophysiology (Bethesda) 78 (6):p2895-903 Dec., **1997**
ISSN: 0022-3077
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Sensory neurons manifest pronounced changes in excitability during maturation, but the factors contributing to this ubiquitous developmental phenomenon are not well understood. To assess the contribution of intrinsic membrane properties to such changes in excitability, in the present study whole cell patch-clamp recordings were made from developing ganglion cells in the intact retina of postnatal rats. During a relatively brief developmental period (postnatal days P7-**P27**) ganglion cells exhibited pronounced changes in the discharge patterns generated by depolarizing current injections. The youngest cells (P7-P17) typically responded to maintained depolarizations with only a single spike or a rapidly adapting discharge pattern. In contrast, the predominant response mode of more mature cells (**P21-P27**) was a series of repetitive discharges that lasted for the duration of the depolarization period, and by P25 all cells responded in this manner. These functional changes characterized all three morphologically defined cell classes identified by intracellular labeling with Lucifer yellow. To determine if expression of the potassium current (I|a) and the kinetics of the Na-channel related to the increased excitability of developing ganglion cells described above, current- and voltage-clamp recordings were made from individual neurons. The different firing patterns manifested by developing retinal ganglion cells did not reflect the presence or absence of the I|a conductance, although cells expressing I|a tended to generate spikes of shorter duration. With maturation the speed of recovery from inactivation of the Na current increased markedly and this related to the increased excitability of developing ganglion cells. Neurons yielding only a single spike to maintained depolarization were characterized by the slowest speed of recovery; cells with rapidly adapting discharges showed a faster recovery and those capable of repetitive firing recovered fastest from Na-channel inactivation. It is suggested that these changes in intrinsic membrane properties may relate to the different functional roles subserved by ganglion cells during development.

1997

20/3,AB/153 (Item 78 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11311822 BIOSIS NO.: 199800093154
Glucocorticoids stimulate **p21** gene expression by targeting multiple transcriptional elements within a steroid responsive region of the **p21**!w!a!f!1!/!c!i!p!1 promoter in **rat** hepatoma cells.
AUTHOR: Cha Helen H; Cram Erin J; Wang Edward C; Huang Art J; Kasler Herbert G; Firestone Gary L(a)
AUTHOR ADDRESS: (a)Dep. Molecular Cell Biol., 591 LSA, Univ. California, Berkeley, CA 94720**USA
JOURNAL: Journal of Biological Chemistry 273 (4):p1998-2007 Jan. 23, **1998**
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Glucocorticoids can induce a G1 arrest in the cell cycle progression of BDS1 **rat** hepatoma cells. In these cells,

dexamethasone, a synthetic glucocorticoids, stimulated a rapid and selective increase in expression of the **p21** cyclin-dependent kinase (CDK) inhibitor mRNA and protein and virtually abolished CDK2 phosphorylation of the retinoblastoma protein. Expression of the **p27** CDK inhibitor, and other G1-acting cell cycle proteins, remained unaffected. Dexamethasone stimulated **p21** promoter activity in a p53-independent manner that required functional glucocorticoid receptors. Transforming growth factor-beta, which also induced a G1 cell cycle arrest of the hepatoma cells, failed to elicit this response. Analysis of 5' deletions of the **p21** promoter uncovered a glucocorticoid responsive region between nucleotides -1481 and -1184, which does not contain a canonical glucocorticoid response element but which can confer dexamethasone responsiveness to a heterologous promoter. Fine mapping of this region uncovered three distinct 50-60-base pair transcriptional elements that likely function as targets of glucocorticoid receptor signaling. Finally, ectopic expression of **p21** had no effect on hepatoma cell growth in the absence of glucocorticoids but facilitated the ability of dexamethasone to inhibit cell proliferation. Thus, our results have established a direct transcriptional link between glucocorticoid receptor signaling and the regulated promoter activity of a CDK inhibitor gene that is involved in the cell cycle arrest of hepatoma cells.

1998

20/3,AB/154 (Item 79 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11249138 BIOSIS NO.: 199800030470
Cell cycle-mediated regulation of hepatic regeneration.
AUTHOR: Ehrenfried John A; Ko Tien C; Thompson E Aubrey; Evers B Mark(a)
AUTHOR ADDRESS: (a)Dep. Surgery, Univ. Texas Med. Branch, 301 University Blvd., Galveston, TX 77555-0533**USA
JOURNAL: Surgery (St Louis) 122 (5):p927-935 Nov., **1997**
ISSN: 0039-6060
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background. Hepatic regeneration after partial hepatectomy (PH) is characterized by a synchronous induction of normally quiescent hepatocytes to reenter the cell cycle, leading to a complete restoration of hepatic mass. Cell cycle progression requires activation of cyclin-dependent kinases (Cdks) that are regulated by cyclins and Cdk inhibitors. Methods. Protein expression of the cyclins (D-type and E), Cdks (Cdk2 and 4), and Cdk inhibitors (**p21** and **p27**) was measured by Western blot after SHAM operation or PH in F344 rats. In addition, Cdk2 associated kinase activity was measured. Results. Rapid induction of D-type and E cyclins, as well as their catalytic partners, Cdk2 and Cdk4, occurred after PH in rats. Complexes containing cyclin E and Cdk2 assembled in the regenerating liver, leading to increased Cdk2-associated kinase activity. The regenerating liver returned to preresection weight by day 7, at which time the Cdk2 activity also returned to SHAM levels. Biphasic induction of the Cdk inhibitor **p21** was observed; the first peak occurred as early as 6 hours after PH, with a subsequent peak in expression occurring at 24 to 72 hours after PH. Conclusions. Taken together, these data support the concept that cyclins, Cdks, and Cdk inhibitors regulate cell cycle progression in the regenerating liver. In addition, the induction of **p21** at two time points suggests that this protein may regulate both early proliferation and subsequent inhibition of hepatocyte regeneration.

1997

20/3,AB/155 (Item 80 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11208700 BIOSIS NO.: 199799829845
Cell cycle regulation of oligodendrocyte differentiation.
AUTHOR: Tikoo R K(a); Casaccia-Bonnefil P; Osterhout D J; Koff A; Chao M V
AUTHOR ADDRESS: (a)Dep. Neurol., Cornell Univ. Med. Coll., New York, NY 10021**USA
JOURNAL: Society for Neuroscience Abstracts 23 (1-2):p1692 **1997**
CONFERENCE/MEETING: 27th Annual Meeting of the Society for Neuroscience New Orleans, Louisiana, USA October 25-30, 1997
ISSN: 0190-5295
RECORD TYPE: Citation
LANGUAGE: English
1997

20/3,AB/156 (Item 81 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11188157 BIOSIS NO.: 199799809302
The geranylgeranyltransferase-I inhibitor GGTI-298 arrests human tumor cells in G-0/G-1 and induces **p21**-WAF1/CIP1/SDI1 in a p53-independent manner.
AUTHOR: Vogt Andreas; Sun Jiazhi; Qian Yimin; Hamilton Andrew D; Sebti Said M(a)
AUTHOR ADDRESS: (a)H. Lee Moffitt Cancer Cent., 12902 Magnolia Dr., Tampa, FL 33612**USA
JOURNAL: Journal of Biological Chemistry 272 (43):p27224-27229 **1997**
ISSN: 0021-9258
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Recently we have shown that in fibroblasts (NIH 3T3 and **Rat** -1 cells) inhibition of protein geranylgeranylation leads to a G-0/G-1 arrest, whereas inhibition of protein farnesylation does not affect cell cycle distribution. Here we demonstrate that in human tumor cells the geranylgeranyltransferase-I (GGTase-I) inhibitor GGTI-298 blocked cells in G-0/G-1, whereas the farnesyltransferase (FTase) inhibitor FTI-277 showed a differential effect depending on the cell line. FTI-277 accumulated Calu-1 and A-549 lung carcinoma and Colo 357 pancreatic carcinoma cells in G-2/M, T-24 bladder carcinoma, and HT-1080 fibrosarcoma cells in G-0/G-1, but had no effect on cell cycle distribution of pancreatic (Panc-1), breast (SKBr 3 and MDAMB-231), and head and neck (A-253) carcinoma cells. Furthermore, treatment of Calu-1, Panc-1, Colo 357, T-24, A-253, SKBr 3, and MDAMB-231 cells with GGTI-298, but not FTI-277, induced the protein expression levels of the cyclin-dependent kinase inhibitor **p21**-WAF. HT-1080 and A-549 cells had a high basal level of **p21**-WAF, and GGTI-298 did not further increase these levels. Furthermore, GGTI-298 also induces the accumulation of large amounts of **p21**-WAF mRNA in Calu-1 cells, a cell line that lacks the tumor suppressor gene p53. There was little effect of GGTI-298 on the cellular levels of another cyclin- dependent kinase inhibitor **p27**-KIP as well as cyclin E and cyclin D1. These results demonstrate that GGTase-I inhibitors arrest cells in G-0/G-1 and induce accumulation of **p21**-WAF in a p53-independent manner and that FTase inhibitors can interfere with cell cycle events by a mechanism that involves neither **p21**-WAF nor **p27**-KIP. The results also point to the potential of GGTase-I inhibitors as agents capable of restoring growth arrest in cells lacking functional p53.

20/3,AB/157 (Item 82 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11176326 BIOSIS NO.: 199799797471
Effects of cyclin D1 overexpression on G1 progression-related events.
AUTHOR: Imoto Masaya; Doki Yuichiro; Jiang Wei; Han Edward Kyu-Ho; Weinstein I Bernard(a)
AUTHOR ADDRESS: (a)Columbia-Presbyterian Cancer Cent., Inst. Cancer Res., Columbia Univ., Coll. Physicians Surgeons**USA
JOURNAL: Experimental Cell Research 236 (1):p173-180 **1997**
ISSN: 0014-4827
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In previous studies (W. Jiang, S. M. Kahn, P. Zhou, Y.-J. Zhang, A. M. Cacace, A. S. Infance, Y. Doi, R. M. Santella, and I. B. Weinstein 1993, Oncogene 8, 3447-3457) we reported that stable overexpression of cyclin D1 in R6 **rat** embryo fibroblasts shortens the G1 phase and impairs growth control. In the present study we examined the effects of cyclin D1 overexpression on other events involved in the G1 to S progression, utilizing the overexpressor cell line R6-ccnD1. We found that when compared to R6 control cells, serum-starved quiescent R6-ccnD1 cells had not only increased levels of the cyclin D1 protein but also increased levels of the cyclin E protein. The latter protein was complexed to phosphorylated cyclin-dependent kinase 2 (CDK2). However, in quiescent serum-starved R6-ccnD1 cells this cyclin E-CKD2 complex lacked in vitro kinase activity due to the presence of a heat-stable inhibitory activity, apparently reflecting the inhibitory effects of the CDK inhibitors (CDKIs) **p21**-WAF1 and **p27**-KIP1. Serum stimulation of the quiescent R6-ccnD1 cells was associated with a loss of this inhibitory activity and a decrease in the levels of the latter two proteins, as the cells progressed through the G1 phase. On the other hand, serum stimulation of the control R6 cells was associated with both induction of cyclin E and increased levels of phosphorylated CDK2 proteins and decreased levels of **p21**-WAF1 and **p27**-KIP1, as the cells progressed through the G1 phase. Thus, even though overexpression of cyclin D1 can induce the expression of cyclin E and phosphorylated CDK2, premature activation of cyclin E-CDK2 kinase activity in quiescent cells or during progression through G1 appears to be blocked by CDKIs. Nevertheless, the R6ccnD1 cells have a shorter G1 phase than the control cells presumably due to the high levels of both cyclin D1 and cyclin E. Taken together, these results indicate that overexpression of cyclin D, which is frequently seen in human tumors, can have complex effects on the expression of other genes that control cell cycle progression.
1997

20/3,AB/158 (Item 83 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11164151 BIOSIS NO.: 199799785296
Linking protein kinase C to cell-cycle control.
AUTHOR: Livneh Etta(a); Fishman Daniel D
AUTHOR ADDRESS: (a)Dep. Immunol. Microbiol., Fac. Health Sci., Ben Gurion Univ., IL-84105 Beer Sheva**Israel
JOURNAL: European Journal of Biochemistry 248 (1):p1-9 **1997**
ISSN: 0014-2956
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Protein kinase C (PKC) isoenzymes are involved in diverse cellular functions, including differentiation, growth control, tumor promotion, and cell death. In recent years, evidence has began to emerge suggesting a role for PKC in cell cycle control. A paper published recently, demonstrating a functional link between PKC and cell cycle control in yeast (Marini, N. J., Meldrum, E., Buehrer, B., Hubberstey, A. V., Stone, D. E., Traynor-Kaplan, A. & Reed, S. I. (1996) EMBO J. 15, 3040-3052), strengthens this data. Thus, the existence of cell-cycle-regulated pathways involving PKC in both yeast and mammals indicate that PKC may be a conserved regulator of cell cycle events that links signal transduction pathways and the cell-cycle machinery. In this paper, we will review current data on the cell cycle components that are targets for PKC regulation. PKC enzymes appear to operate as regulators of the cell cycle at two sites, during G1 progression and G2/M transition. In G1, the overall effect of PKC activation is inhibition of the cell cycle at mid to late G1. This cell cycle inhibition correlates with a blockage in the normal phosphorylation of the tumor suppressor retinoblastoma Rb protein, presumably through an indirect mechanism. The reduced activity of the cyclin-dependent kinase, Cdk2, appears to be the major effect of PKC activation in various cell systems. This may also underlie the inhibition of Rb phosphorylation exhibited by PKC activation. Several mechanisms were described in different studies on the regulation of Cdk2 activity by PKC; reduced Cdk-activating kinase activity, diminished expression of the Cdk2 partners cyclins E or A, and the increased expression of the cyclin-dependent inhibitors, **p21**-WAF1 and **p27**-KIP1, which are capable of binding to cyclin/Cdk2 complexes. PKC enzymes were also shown to play a role in G2/M transition. Among the suggested mechanisms is suppression of Cdc2 activity. However, most of the published data strongly implicate PKC in lamin B phosphorylation and nuclear envelope disassembly.

1997

20/3,AB/159 (Item 84 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11162375 BIOSIS NO.: 199799783520
Cell cycle in alveolar epithelial type II cells: Integration of Matrigel and KGF.
AUTHOR: Buckley Sue; Driscoll Barbara; Anderson Kathryn D; Warburton David (a)
AUTHOR ADDRESS: (a)Dep. Surgery Pediatrics, Childrens Hosp. Los Angeles, 4650 Sunset Blvd., MS35, Los Angeles, CA 9**USA
JOURNAL: American Journal of Physiology 273 (3 PART 1):pL572-L580
1997
ISSN: 0002-9513
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The regulation of cell cycle control in alveolar epithelial type II cells (AEC2) in response to peptide growth factors and extracellular matrix signals is not well understood. Herein, we have determined that, in adult **rat** AEC2 in primary culture on Engelbreth-Holm-Swarm biomatrix (Matrigel) in the presence of keratinocyte growth factor, the expression of key cell cycle control elements, including cyclins A and D and cyclin-dependent kinases (cdk) 1 and 4, is increased and that retinoblastoma protein (pRb) phosphorylation is also increased, with a corresponding decrease in the expression of p53 and the cdk inhibitors (cdkis) **p21**-WAF1/CIP1 and **p27**-KIP-1 compared with cells cultured on plastic. The Matrigel biomatrix-KGF culture conditions were also associated with an enhanced proliferative response, as measured by

fluorescent-activated cell sorter analysis, thymidine incorporation into DNA, and proliferating cell nuclear antigen expression. The enhanced proliferation occurred with neither a soluble extract of Matrigel biomatrix nor with other simple biological matrices. We conclude that coordinated induction of key cyclins and cdks, with the concomitant suppression of key negative cell cycle regulators, occurs in AEC2 on Matrigel biomatrix in the presence of KGF. We speculate that the balance between cyclin and cdk activation and cdki suppression in AEC2 serves to integrate the combined influences of biomatrix and KGF signaling on pRb phosphorylation, thereby controlling transit through S phase of the cell cycle. Conversely, AEC2 express high levels of cdkis and p53 at rest in G-1 phase. The latter finding may explain the quiescent state of normal adult AEC2 in vivo.

1997

20/3,AB/160 (Item 85 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11128534 BIOSIS NO.: 199799749679
Loss of cell adhesion to substratum up-regulates **p21**-Cip1/WAF1 expression in BALB/c 3T3 fibroblasts.
AUTHOR: Kuzumaki Takejiro(a); Ishikawa Kiichi
AUTHOR ADDRESS: (a)Dep. Biochemistry, Yamagata Univ. Sch. Med., Iida-nishi, Yamagata 990-23**Japan
JOURNAL: Biochemical and Biophysical Research Communications 238 (1):p 169-172 **1997**
ISSN: 0006-291X
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Cell adhesion to substratum is essential for the transition of G1 to S phase in **mouse** BALB/c 3T3 fibroblast cell cycle. Loss of cell adhesion in late G1 phase caused blockage of the G1/S phase transition and repression of cyclin E-associated cyclin-dependent kinase-2 (CDK2) activity. A CDK2 inhibitor abundant in quiescent cells, **p27**-Kip1, was down-regulated by growth factors in serum, and this down-regulation was partially prevented by loss of cell adhesion. Another CDK2 inhibitor, **p21**-Cip1/WAF1, which was undetectable in quiescent cells, was markedly induced by loss of cell adhesion. In exponentially growing cells, loss of cell adhesion also induced **p21**-Cip1/WAF1 expression but did not affect the abundance of **p27**-Kip1. These results suggest that loss of cell adhesion to substratum up-regulates **p21**-Cip1/WAF1 expression, which plays an essential role for arresting the BALB/c 3T3 fibroblast cell cycle.

1997

20/3,AB/161 (Item 86 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11117633 BIOSIS NO.: 199799738778
G1 arrest and high expression of cyclin kinase and apoptosis inhibitors in accumulated activated/memory phenotype CD4+ cells of older lupus mice.
AUTHOR: Sabzevari Helen; Propp Stephanie; Kono Dwight H; Theofilopoulos Argyrios N(a)
AUTHOR ADDRESS: (a)Immunol. Dep., Scripps Res. Inst., 10550 N. Torrey Pines Rd./IMM3, La Jolla, CA 92037**USA
JOURNAL: European Journal of Immunology 27 (8):p1901-1910 **1997**
ISSN: 0014-2980
RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: A general characteristic of lupus-prone mice (and humans) is the expedited accumulation of large numbers of presumably self-reactive activated/memory phenotype T cells. The mechanism by which these cells escape apoptosis has not been defined. We used activated/memory phenotype CD4+ cells from male BXSB mice with early-life severe lupus-like disease to investigate cell cycle status and apoptosis susceptibility, and to determine the role of corresponding genes in survival of these cells. In vitro acridine orange staining indicated that most of the rapidly accumulating memory phenotype CD4+ T cells of 4-month-old male BXSB mice are G1 arrested. Long-term bromodeoxyuridine in vivo labeling also showed that with advanced age, there was a shift of the CD4+ CD44-hi male cells from predominantly cycling to predominantly noncycling. Moreover, the CD4+ CD44-hi cells of older males were refractory to anti-CD3-induced proliferation and apoptosis. Using a multiprobe RNase protection assay encompassing riboprobe panels for cell cycle and apoptosis-related genes, we found that these cells exhibited high expression of certain members of the Ink4 (p18-Ink4C) and Cip/Kip (**p21**-Cip1) families of cyclin kinase inhibitors as well as of the apoptosis-inhibiting BCl-x-L gene. Western blot analysis confirmed increased levels of BCl-x-L and **p21**-Cip1, and also identified increases in another cyclin kinase inhibitor, **p27**-Kip1. We propose that in autoimmunity, self-reactive CD4+ cells are subjected to successive rounds of activation/division that eventually lead to a build-up in cyclin-dependent kinase inhibitors. Once high levels of such inhibitors are reached, they cause refractoriness to further activation, impaired cell cycle entry and resistance to apoptosis, a situation akin to replicative senescence.

1997

20/3,AB/162 (Item 87 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11115095 BIOSIS NO.: 199799736240
Involvement of the cell cycle inhibitor CIP1/WAF1 in lung alveolar epithelial cell growth arrest induced by glucocorticoids.
AUTHOR: Corroyer Sophie; Nabeyrat Elodie; Clement Annick(a)
AUTHOR ADDRESS: (a)Physiology Dep., Trousseau Hosp., 26 Ave. Dr. Netter, 75012 Paris**France
JOURNAL: Endocrinology 138 (9):p3677-3685 **1997**
ISSN: 0013-7227
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Glucocorticoids are known to impair the postnatal development of lung parenchyma by altering the formation of alveoli, and from the current understanding of the processes controlling the growth of the alveolar structure, it is likely that this impairment relies in large part on alteration of alveolar epithelial cell replication. From recent studies on the modulation of cell proliferation by glucocorticoids, it appears that events associated with the G1 phase of the cell cycle are a major target for the actions of these hormones. To gain some insights into the mechanisms involved in the growth arrest of lung alveolar epithelial cells by glucocorticoids, we focused in the present study on the effects of these hormones on the expression of the G1 cyclins and their cell cycle-dependent kinases (CDKs). We observed that when cells were blocked in their proliferation by dexamethasone treatment, no changes in the expression of the various G1 cyclins, D1, D2, D3, or E, could be documented. Also, the levels of CDK2 and CDK4 in glucocorticoid-treated cells did not exhibit significant modifications compared with the levels in proliferating cells. Evaluation of the activity of cyclin-CDK complexes showed that activation of cyclin D-CDK4

was not modified by dexamethasone. By contrast, differences in the activity of cyclin E-CDK2 complexes were found, with a pro[illegible]nd decrease in the extracts of cells growth arrested by dexamethasone. Studies of the factors potentially implicated in the inactivation of these complexes strongly suggested a role for p2-CIP1, as a dramatic accumulation of this protein was observed in cells treated with dexamethasone. Moreover, changes in **p21**-CIP1 expression appeared to be controlled mostly at the posttranscriptional level. Interestingly, a decrease in the levels of **p27**-KIP1 could be observed. These results indicate that glucocorticoids block entry of alveolar epithelial cells into S phase by specifically altering the activation of cyclin E-CDK2 complexes through induction of the CDK inhibitor **p21**-CIP1.

1997

20/3,AB/163 (Item 88 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11111660 BIOSIS NO.: 199799732805
Raf-induced proliferation or cell cycle arrest is determined by the level of Raf activity with arrest mediated by **p21**-Cip1.
AUTHOR: Woods Douglas; Parry David; Cherwinski Holly; Bosch Elizabeth; Lees Emma; McMahon Martin(a)
AUTHOR ADDRESS: (a)Dep. Cell Signaling, DNAX Res. Inst., 901 California Ave., Palo Alto, CA 94304**USA
JOURNAL: Molecular and Cellular Biology 17 (9):p5598-5611 **1997**
ISSN: 0270-7306
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The Raf family of protein kinases display differences in their abilities to promote the entry of quiescent NIH 3T3 cells into the S phase of the cell cycle. Although conditional activation of DELTA-A-Raf:ER promoted cell cycle progression, activation of DELTA-Raf-1:ER and DELTA-B-Raf:ER elicited a G-1 arrest that was not overcome by exogenously added growth factors. Activation of all three DELTA-Raf:ER kinases led to elevated expression of cyclin D1 and cyclin E and reduced expression of **p27**-Kip1. However, activation of DELTA-B-Raf:ER and DELTA-Raf-1:ER induced the expression of **p21** -Cip1, whereas activation of DELTA-A-Raf:ER did not. A catalytically potentiated form of DELTA-A-Raf:ER, generated by point mutation, strongly induced **p21**-Cip1 expression and elicited cell cycle arrest similarly to DELTA-B-Raf:ER and DELTA-Raf-1:ER. These data suggested that the strength and duration of signaling by Raf kinases might influence the biological outcome of activation of this pathway. By titration of DELTA-B-Raf:ER activity we demonstrated that low levels of Raf activity led to activation of cyclin D1-cdk4 and cyclin E-cdk2 complexes and to cell cycle progression whereas higher Raf activity elicited cell cycle arrest correlating with **p21**-Cip1 induction and inhibition of cyclin-cdk activity. Using green fluorescent protein-tagged forms of DELTA-ARaf-1:ER in primary **mouse** embryo fibroblasts (MEFs) we demonstrated that **p21**-Cip1 was induced by Raf in a p53-independent manner, leading to cell cycle arrest. By contrast, activation of Raf in **p21**-Cip1-/- MEFs led to a robust mitogenic response that was similar to that observed in response to platelet-derived growth factor. These data indicate that, depending on the level of kinase activity, Raf can elicit either cell cycle progression or cell cycle arrest in **mouse** fibroblasts. The ability of Raf to elicit cell cycle arrest is strongly associated with its ability to induce the expression of the cyclin-dependent kinase inhibitor **p21**-Cip1 in a manner that bears analogy to alpha-factor arrest in Saccharomyces cerevisiae. These data are consistent with a role for Raf kinases in both proliferation and differentiation of mammalian cells.

1997

20/3,AB/164 (Item 89 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11093647 BIOSIS NO.: 199799714792
Cyclin kinase inhibitors are increased during experimental membranous nephropathy: Potential role in limiting glomerular epithelial cell proliferation in vivo.
AUTHOR: Shankland Stuart J(a); Floege Juergen; Thomas Susan E; Nangaku Masaomi; Hugo Christian; Pippin Jeffrey; Henne Kevin; Hockenberry David M ; Johnson Richard J; Couser William G
AUTHOR ADDRESS: (a)Div. Nephrol., Univ. Wash., P.O. Box 356521, Seattle, WA 98195**USA
JOURNAL: Kidney International 52 (2):p404-413 **1997**
ISSN: 0085-2538
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The inadequate proliferative response of the visceral glomerular epithelial cell (GEC) following injury in vivo may contribute to the development of progressive glomerulosclerosis in many forms of glomerular disease. Cell proliferation is ultimately controlled by cell-cycle regulatory proteins, including cyclins that bind to cyclin dependent kinases (CDK), and the active complex formed is necessary for progression through the cell-cycle. By inhibiting cyclin-CDK complexes, cyclin kinase inhibitors arrest the cell-cycle and prevent proliferation. To determine the mechanisms that may be responsible for the lack of GEC proliferation in vivo, we examined GEC expression of specific cell-cycle proteins in normal rats and in the passive Heymann nephritis (PHN) model of membranous nephropathy, where the GEC are the target of complement-mediated injury. Following antibody deposition and complement activation there was a marked up-regulation in the cyclin kinase inhibitors **p21** and **p27** in rats with PHN. By associating with cyclin A-CDK2 complexes, **p21** and **p27** limited the kinase activity of CDK2. Giving bFGF to rats with PHN was associated with an increase in GEC mitosis and ploidy and a decrease in expression of **p21**, but not CDK2 or **p27**. Furthermore, apoptosis was not present in PHN, but was increased in rats given bFGF. In conclusion, this study shows that the low proliferative capacity of the GEC in vivo in response to immune injury may be due to an increase in the expression of specific cyclin kinase inhibitors. The increase in mitosis in PHN rats given bFGF may be due to a decrease in **p21**. Thus, changes in cell cycle regulatory proteins may regulate the response of GEC to injury and underlie the development of progressive glomerulosclerosis in diseases of the GEC.

1997

20/3,AB/165 (Item 90 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11023752 BIOSIS NO.: 199799644897
Activin A induction of cell-cycle arrest involves modulation of cyclin D2 and **p21**-CIP1/WAF1 in plasmacytic cells.
AUTHOR: Yamato Kenji(a); Koseki Takeyoshi; Ohguchi Masahiro; Kizaki Masahiro; Ikeda Yasuo; Nishihara Tatsuji
AUTHOR ADDRESS: (a)Dep. Oral Sci., Natl. Inst. Infect. Dis., 1-23-1 Toyama, Shinjuku-ku, Tokyo 162**Japan
JOURNAL: Molecular Endocrinology 11 (8):p1044-1052 **1997**

ISSN: 0888-8809
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Activins, members of the transforming growth factor-beta family, have been implicated in the regulation of growth and differentiation of various types of cells. We have recently found that activin A induces apoptotic cell death of plasmacytic cells including B cell hybridoma cells and myeloma cells. In the present study, we demonstrated that activin A caused cell-cycle arrest in the G1 phase before appearance of apoptotic cells in **mouse** B cell hybridoma cells. Phosphorylation of retinoblastoma protein (Rb) and in vitro Rb kinase activity of cyclin-dependent kinase (CDK)4 was inhibited in activin A-treated cells. Analysis of expression of genes regulating Rb phosphorylation revealed that activin A suppressed cyclin D2, the sole D-type cyclin gene expressed in the hybridoma cells, and activated **p21**-CIP1/WAF1 but had no effect on expression of cyclin-dependent kinases (CDK2, CDK4, CDK6) and other CDK inhibitors (**p27**-KIP1, p16-INK4a, p15-INK4b). Modulation of cyclin D2 and **p21**-CIP1/WAF1 expression resulted in a decrease in level of cyclin D2-CDK4 complex and an increase in level of CDK4 complexed with **p21**-CIP1/WAF1. Moreover, overexpression of cyclin D2 partially abrogated inhibition of Rb phosphorylation and G1 arrest in the hybridoma cells.

1997

20/3,AB/166 (Item 91 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11018129 BIOSIS NO.: 199799639274
Cloning and characterization of **rat p27**-Kip1, a cyclin-dependent kinase inhibitor.
AUTHOR: Nomura Hajime; Sawada Yukiharu; Fujinaga Kei; Ohtaki Sachiya(a)
AUTHOR ADDRESS: (a)Dep. Lab. Med., Miyazaki Med. Coll., Miyazaki, Kiyotake 889-16**Japan
JOURNAL: Gene (Amsterdam) 191 (2):p211-218 **1997**
ISSN: 0378-1119
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Cyclin-dependent kinase (Cdk) inhibitors play significant roles in the cell cycle control of various biological phenomena. To characterize the role of Cdk inhibitors in **rat** cells, we isolated a cDNA encoding **rat p27**-Kip1, a 27-kDa Cdk inhibitor. The 1.04-kb cDNA of **rat p27** contained an open reading frame of 197 amino acids that shared high homology with mammalian **p27** and significant homology with mammalian **p21**-Cip1 and p57-Kip2. **p27** mRNA was detected in most **rat** tissues and cell lines. The levels of **p27** protein expression were similar in **rat** cell lines transformed by E1A and in normal cells. **Rat p27** was able to interact with Cdk 2/4 and cyclin A/D in **rat** cells, but the amounts of **rat p27** in Cdk2 complexes were different between transformed cells and normal cells. Thus, the formation of stable complexes of **rat p27** may be modulated by E1A. **Rat p27** protein could inhibit the increased Cdk2-associated kinase activity in transformed **rat** cells.

1997

20/3,AB/167 (Item 92 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11015591 BIOSIS NO.: 1997[redacted]36736
Down-regulation of the CDKIs, **p21** and **p27**, during cardiac hypertrophy.
AUTHOR: Brooks Gavin; Li Jian-Mei
AUTHOR ADDRESS: Cardiovascular Res., Rayne Inst., St. Thomas' Hosp., London**UK
JOURNAL: Journal of Molecular and Cellular Cardiology 29 (5):pA61 **1997**
CONFERENCE/MEETING: XVIII European Section Meeting of the International Society for Heart Research Versailles, France July 2-5, 1997
ISSN: 0022-2828
RECORD TYPE: Citation
LANGUAGE: English
1997

20/3,AB/168 (Item 93 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11015513 BIOSIS NO.: 199799636658
Cell cycle regulatory molecule expression during heart development.
AUTHOR: Burton Paul B J; Yacoub Magdi H; Barton Paul J R
AUTHOR ADDRESS: Cardiothoracic Surg., Imperial Coll. Sch. Med., Natl. Heart and Lung Inst., Dovehouse St., London SW**UK
JOURNAL: Journal of Molecular and Cellular Cardiology 29 (5):pA41 **1997**
CONFERENCE/MEETING: XVIII European Section Meeting of the International Society for Heart Research Versailles, France July 2-5, 1997
ISSN: 0022-2828
RECORD TYPE: Citation
LANGUAGE: English
1997

20/3,AB/169 (Item 94 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11015425 BIOSIS NO.: 199799636570
Cip/Kip cyclin-dependent kinase inhibitor (CDKI) expression during cardiac myocyte development.
AUTHOR: Poolman Robert A; Brooks Gavin
AUTHOR ADDRESS: Rayne Inst., St. Thomas' Hosp., London**UK
JOURNAL: Journal of Molecular and Cellular Cardiology 29 (5):pA19 **1997**
CONFERENCE/MEETING: XVIII European Section Meeting of the International Society for Heart Research Versailles, France July 2-5, 1997
ISSN: 0022-2828
RECORD TYPE: Citation
LANGUAGE: English
1997

20/3,AB/170 (Item 95 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10989497 BIOSIS NO.: 199799610642
Dl-propranolol negatively regulates the transcription of proliferating cell nuclear antigen (PCNA)-gene and thereby suppresses DNA synthesis in regenerating **rat** liver.
AUTHOR: Hong Jeong-Ho; Hwang Eun Sook; Lee Chang Ho; Lee Yong Hee; Lee Seung Ki(a)

AUTHOR ADDRESS: (a)Coll. Pharm., Seoul Natl. Univ., Seoul 151-742**South Korea
JOURNAL: Biochemistry and Molecular Biology International 42 (1):p103-112 **1997**
ISSN: 1039-9712
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Previous reports have suggested that dl-propranolol (PRL) suppresses DNA synthesis by blocking cAMP-mediated signaling in **rat** liver after partial hepatectomy (PH). Here, we examined if PRL negatively regulates the expression of genes involved in cell cycle progression. Immunoblotting assays showed that the protein levels of cyclins A and E, Cdk2, **p21**-WAF1, and **p27**-KIP1 did not significantly change in liver tissues from either vehicle- or PRL- injected rats after PH. However, the levels of PCNA and PCNA-MRNA markedly decreased in the remnant liver in response to PRL-injection. Similarly, PCNA-CRE binding activity of nuclear 43kDa CREB was suppressed, although the protein levels were not altered. We suggest that PRL negatively regulates the PCNA-gene transcription by interfering with the cAMP/PKA-mediated induction of CREB binding to the CRE-sequences and thereby suppresses DNA synthesis in regenerating **rat** liver.

1997

20/3,AB/171 (Item 96 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10975953 BIOSIS NO.: 199799597098
Time course comparison of cell-cycle protein expression following partial hepatectomy and WY14,643-induced hepatic cell proliferation in F344 rats.
AUTHOR: Rininger J A(a); Goldsworthy T L; Babish J G
AUTHOR ADDRESS: (a)Paracelsian Inc., Section Cellular Physiol., Langmuir Labs., Box 1005, 95 Brown Rd., Ithaca, NY **USA
JOURNAL: Carcinogenesis (Oxford) 18 (5):p935-941 **1997**
ISSN: 0143-3334
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: During recent years, there has been an extensive research focus in the area of cell-cycle control in eukaryotes and the relationship that exists between cell proliferation and cancer. The eukaryotic cell-cycle is governed by signal transduction pathways mediated by complexes of cyclin dependent kinases (CDK) and their partner cyclin proteins. This study was performed to identify differences in cell-cycle control protein expression following physical and chemical stimuli of hepatic cell growth. Protein levels of cell cycle mediators, cyclin dependent kinases (CDK 1,2,4,5), cyclin proteins (A,B,D1-D3 and E), proliferating cell nuclear antigen (PCNA), tumor suppressor proteins (p53 and Rb), and CDK inhibitory proteins (p16-Ink4, **p21**-Waf1 and **p27**-Kip1) were examined in F344 rats following 70% partial hepatectomy or a single dose of WY14,643 over 96- and 48-h time courses, respectively. CDK1 (p34-cdc2) and PCNA protein concentrations, quantified by ELISA, were significantly increased beginning at the 24-h time point and maximal at 48 h (6.9- and 3.7-fold for partial hepatectomy and 4.2- and 3.3-fold for WY14,643, respectively). Differential effects were observed with the G1 cell-cycle mediators CDK4, CDK5, and cyclin D3, **p21**-Waf1 and **p27**-Kip1 CDK inhibitory protein concentrations rose in accordance with the induction of DNA synthesis and histone H1 kinase activity. In addition, there were dramatic differences in p53 protein expression patterns following partial hepatectomy versus WY14,643 dosing. Because non-genotoxic hepatocarcinogens are known to induce cellular proliferation, data generated from this study may aid in elucidating the

specific hepatocarcinogeni[redacted] signal transduction pathways st[redacted]mulated by non-genotoxic carcinogens[redacted]

1997

20/3,AB/172 (Item 97 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10973660 BIOSIS NO.: 199799594805
Regulation of apoptosis and cell cycle arrest by Zac1, a novel zinc finger protein expressed in the pituitary gland and the brain.
AUTHOR: Spengler Dietmar; Villalba Martin; Hoffmann Anke; Pantaloni Colette ; Houssami Souheir; Bockaert Joel; Journot Laurent(a)
AUTHOR ADDRESS: (a)CNRS UPR-9023, Mecanismes Mol. Communications Cell., CCIPE, 141 rue de la Cardonille, F-34094 Mo**France
JOURNAL: EMBO (European Molecular Biology Organization) Journal 16 (10):p 2814-2825 **1997**
ISSN: 0261-4189
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The proliferation rate of a cell population reflects a balance between cell division, cell cycle arrest, differentiation and apoptosis. The regulation of these processes is central to development and tissue homeostasis, whereas dysregulation may lead to overt pathological outcomes, notably cancer and neurodegenerative disorders. We report here the cloning of a novel zinc finger protein which regulates apoptosis and cell cycle arrest and was accordingly named Zac1. In vitro Zac1 inhibited proliferation of tumor cells, as evidenced by measuring colony formation, growth rate and cloning in soft agar. In vivo Zac1 abrogated tumor formation in nude mice. The antiproliferative activity of Zac1 was due to induction of extensive apoptosis and of G-1 arrest, which proceeded independently of retinoblastoma protein and of regulation of **p21** -WAF1/Cip1, **p27**-Kip1, p57-Kip2 and p16-INK4a expression.
Zac1-mediated apoptosis was unrelated to cell cycle phase and G-1 arrest was independent of apoptosis, indicating separate control of apoptosis and cell cycle arrest. Zac1 is thus the first gene besides p53 which concurrently induces apoptosis and cell cycle arrest.

1997

20/3,AB/173 (Item 98 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10926086 BIOSIS NO.: 199799547231
Glucocorticoid inhibition of fibroblast proliferation and regulation of the cyclin kinase inhibitor **p21**-Cip1.
AUTHOR: Ramalingam Arivudainambi; Hirai Aki; Thompson E Aubrey(a)
AUTHOR ADDRESS: (a)Dep. Human Biol. Chem. Genetics, Univ. Texas Med. Branch, Galveston, TX 77555-0645**USA
JOURNAL: Molecular Endocrinology 11 (5):p577-586 **1997**
ISSN: 0888-8809
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Glucocorticoids inhibit the proliferation of fibroblastic cells in vivo and in culture; however, the molecular mechanism that accounts for this effect has remained obscure. We have undertaken to elucidate the mechanism whereby glucocorticoids decrease the rate of proliferation of **mouse** L929 fibroblastic cells. Addition of dexamethasone to mid-log phase fibroblasts prolongs G1 phase. This increase in the G1 interval is

associated with, and probably due to, inhibition of phosphorylation of the product of the Rb-1 tumor suppressor gene, pRb. Inhibition of pRb phosphorylation by cyclin D-dependent kinases can be demonstrated in vitro. Nevertheless, there is no detectable change in the expression of cyclin D1, cyclin D2, or cyclin D3. Cyclin-dependent kinase-4 (Cdk4) and Cdk6 are not down-regulated in L929 cells after addition of glucocorticoids, and the abundance of cyclin D/Cdk4 complexes does not change. Inhibition of pRb kinase activity is associated with an increase in the abundance of one of the Cdk inhibitors, **p21**-Cip1. The abundance of another cyclin kinase inhibitor, **p27**-Kip1, remains constant. The amount of Cdk4 that is bound to **p21**-Cip1 increases rapidly after addition of dexamethasone, and the activity of Cdk4-pRb kinase decreases in parallel. These results indicate that glucocorticoid inhibition of fibroblast proliferation is due to induction of **p21** -Cip1, which binds to and inactivates cyclinD/Cdk4 complexes. The abundance of **p21** mRNA increases about 5-fold within 2 h after addition of dexamethasone. This effect does not obtain in L929 mutants that are null for the glucocorticoid receptor, and a variant that expresses the glucocorticoid receptor from a tetracycline-repressible expression vector demonstrates induction of **p21** mRNA only in the absence of tetracycline. Cycloheximide does not block induction of **p21** mRNA, and dexamethasone has no detectable effect on the apparent rate of degradation of **p21** mRNA. Nuclear run-on transcription of the Cip1 gene increases within 2 h after addition of dexamethasone. This effect can be blocked by tetracycline-mediated repression of the glucocorticoid receptor.

1997

20/3,AB/174 (Item 99 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10904852 BIOSIS NO.: 199799525997
Murine hepatic p53, RB, and CDK inhibitory protein expression following acute 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposure.
AUTHOR: Rininger Joseph A(a); Stoffregen Dana A; Babish John G
AUTHOR ADDRESS: (a)Paracelsian Inc. Langmuir Lab., Box 1005, Cornell Technology Park, 95 Brown Road, Ithaca, NY 145**USA
JOURNAL: Chemosphere 34 (5-7):p1557-1568 **1997**
ISSN: 0045-6535
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: This study examined the expression of murine hepatic tumor suppressor and cell cycle inhibitory proteins in response to acute 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) dosing in Balb/c mice. Elevations in expression of p53, retinoblastoma (Rb) protein, p16-Ink4, **p21**-Waf1 and **p27**-Kip1 were observed six days after a single dose of 0.25, 0.5, 1 or 2 mu-g TCDD/kg. These data suggest that the TCDD-induced inhibition of hepatocyte proliferation in vivo could be attributed to the expression of cell cycle inhibitory proteins.

1997

20/3,AB/175 (Item 100 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10797475 BIOSIS NO.: 199799418620
Induction of cyclins E and A in response to mitogen removal: A basic alteration associated with the arrest of differentiation of C2 myoblasts transformed by simian virus 40 large T antigen.

AUTHOR: Tedesco Donato; Bar[redacted] Livio; Fischer-Fantuzzi Lia; V[redacted]o Cesare(a)
AUTHOR ADDRESS: (a)Istitut[redacted] Biologia Cellulare del CNR, V[redacted]e Marx 43, 00137 Rome**Italy
JOURNAL: Journal of Virology 71 (3):p2217-2224 **1997**
ISSN: 0022-538X
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We previously showed that C2 myoblasts transformed by simian virus 40 large T antigen (SVLT) stop the myogenic process after the induction of myogenin and of high Rb levels; the induced Rb, however, becomes notably phosphorylated. We have analyzed the protein levels and activities of cyclin-dependent kinases (cdks) in untransformed C2 cells and in transformants of either SVLT or the cytoplasmic mutant NKT1 (which permits differentiation) upon a shift from growth medium (GM) to mitogen-poor differentiation medium (DM). After the shift, cdk4 levels remained constant and cdk6 levels decreased in all cell types; cdk2 minimally increased only in SVLT cells. Cyclin D1 was downregulated in DM in all cell types, and cyclin D3 was upregulated (albeit less strongly in SVLT cells than in the others). In contrast, a dramatic difference between SVLT cells and the other cells was observed for cyclins E and A, which essentially disappeared (as protein and RNA) in normal C2 and NKT1 cells upon the shift from GM to DM, whereas they increased in SVLT cells. Concurrently, cdk2 activity ceased in C2 and NKT1 cells in DM, whereas it persisted at 20% of the GM level in SVLT cells. cdk4 activity was detectable in all cells only in GM. Cyclin E and A induction thus appeared to sustain enough Rb phosphorylation to interfere with tissue-specific expression. with cdk activity not high enough to activate cyclin self-regulation. In DM, cdk2 complexed to D3 was underphosphorylated in all cells, and SVLT allowed strong inductions of **p21** and **p27** without affecting their complexes with cdks.

1997

20/3,AB/176 (Item 101 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10754762 BIOSIS NO.: 199799375907
Changes in the expression of cell cycle regulators during **rat** liver regeneration after partial hepatectomy.
AUTHOR: Cho Hyeseong; Lim In Kyoung; Lee Jae-Ho(a)
AUTHOR ADDRESS: (a)Dep. Biochem., Sch. Med., Ajou Univ., Suwon 442-749** South Korea
JOURNAL: Experimental & Molecular Medicine 28 (4):p187-191 **1996**
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The changes of cell cycle regulators which may trigger G-0 to G-1 transition during liver regeneration have been examined. In vivo thymidine uptake indicated that S phase began about 18 h and the peak of DNA synthesis appeared from 21 to 24 h after partial hepatectomy. Various time-points from Go to mid-S-phase were selected within 24 h after partial hepatectomy and the expression levels of cyclins, cyclin-dependent kinase (Cdk) and cyclin-dependent kinase inhibitors (CKIs) were examined by Northern and Western analysis. Both cyclin D1 mRNA and protein increased at 15 h after operation. Cyclin E mRNA was first detected at 12 h and continued to increase until 21 h, whereas expression of cyclin B mRNA was first observed at 21 h. Expression of Cdk4 mRNA in normal **rat** liver was clearly detectable, increased significantly at 9 h after resection, and remained increased up to 24 h. On the other hand, an increase in Cdk4 protein was observed as early as 3 h after the surgery and reached plateau at 18 h. We next examined expression of CKIs which may regulate activity of cyclin/Cdk complex

during liver regeneration. **p27**-KIP1 protein was detected in normal **rat** liver whereas **p21**-CIP[redacted]rotein was not. Expression of [redacted] **p21**-C1P-1 protein appeared as early as 3 h and h.

1996

20/3,AB/177 (Item 102 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10733192 BIOSIS NO.: 199799354337
Involvement of **p21**-cip-1 and **p27**-kip-1 in the molecular mechanisms of steel factor induced proliferative synergy in vitro and of p-21cip-1 in the maintenance of stem/progenitor cells in vivo.
AUTHOR: Mantel C(a); Luo Z; Canfield J; Braun S; Deng C; Broxmeyer H E
AUTHOR ADDRESS: (a)Dep. Med., Indiana Univ. Sch. Med., Indianapolis, IN** USA
JOURNAL: Blood 88 (10 SUPPL. 1 PART 1-2):p539A **1996**
CONFERENCE/MEETING: Thirty-eighth Annual Meeting of the American Society of Hematology Orlando, Florida, USA December 6-10, 1996
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English
1996

20/3,AB/178 (Item 103 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

10713416 BIOSIS NO.: 199799334561
The absence of **p21**-Cip1/WAF1 alters keratinocyte growth and differentiation and promotes ras-tumor progression.
AUTHOR: Missero Caterina; Di Cunto Ferdinando; Kiyokawa Hiroaki; Koff Andrew; Dotto G Paolo(a)
AUTHOR ADDRESS: (a)Cutaneous Biol. Res. Cent., Harvard Med. Sch., Boston, MA 02129**USA
JOURNAL: Genes & Development 10 (23):p3065-3075 **1996**
ISSN: 0890-9369
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: **p21**-Cip1/WAF1 was the first cyclin-dependent kinase (CDK) inhibitor to be identified, as a mediator of p53 in DNA damage-induced growth arrest, cell senescence, and direct CDK regulation. **p21** may also play an important role in differentiation-associated growth arrest, as its expression is augmented in many terminally differentiating cells. A general involvement of **p21** in growth/differentiation control and tumor suppression has been questioned, as mice lacking **p21** undergo a normal development, harbor no gross alterations in any of their organs, and exhibit no increase in spontaneous tumor development. However, a significant imbalance between growth and differentiation could be unmasked under conditions where normal homeostatic mechanisms are impaired. We report here that primary keratinocytes derived from **p21** knockout mice, transformed with a ras oncogene, and injected subcutaneously into nude mice exhibit a very aggressive tumorigenic behavior, which is not observed with wild-type control keratinocytes nor with keratinocytes with a disruption of the closely related **p27** gene. **p21** knockout keratinocytes tested under well-defined in vitro conditions show a significantly increased proliferative potential, which is also observed but to a lesser extent with **p27** knockout cells. More profound differences were found in the differentiation behavior of **p21** versus **p27** knockout keratinocytes, with **p21** (but not **p27**) deficiency causing a drastic down-modulation of

differentiation markers linked with the late stages of the keratinocyte terminal differentiation program. Thus, our results reveal so far undetected role of **p21** in tumor suppression, demonstrate that this function is specific as it cannot be attributed to the closely related **p27** molecule, and point to an essential involvement of **p21** in terminal differentiation control, which may account for its role in tumor suppression.

1996

20/3,AB/179 (Item 104 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10706017 BIOSIS NO.: 199799327162
Expression of G1 cyclins, cyclin-dependent kinases, and cyclin-dependent kinase inhibitors in androgen-induced prostate proliferation in castrated rats.
AUTHOR: Chen Yian; Robles Ana I; Martinez Luis A; Liu Feng; Gimenez-Conti Irma B; Conti Claudio J(a)
AUTHOR ADDRESS: (a)Univ. Texas M. D. Anderson Cancer Cent., Sci. Park-Res. Div., PO Box 389, Smithville, TN 78957**USA
JOURNAL: Cell Growth & Differentiation 7 (11):p1571-1578 **1996**
ISSN: 1044-9523
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Androgen induces prostate cell proliferation in the castrated **rat**. We hypothesized that G1 cyclins, cyclin-dependent kinases (cdk), and cdk inhibitors mediate this cellular response to mitogenic signals. In this study, induction of cyclins D1, D2, D3, E, and cdks 2, 4, and 6 expression was observed at various time points during testosterone replacement in the ventral prostate of castrated rats. The induction followed prostate epithelium proliferation, which peaked at 48 h and decreased at 120 h during the treatment. The study of cyclin/cdk complex formation revealed that more cyclin D1/cdk4 and cyclin D1/cdk6 complexes were formed at 48 h than at 120 h of treatment, but cyclin D1/cdk2 complexes remained the same. Furthermore, both hyperphosphorylated and hypophosphorylated forms of Rb were detected at 48 h, but only the hypophosphorylated form was detected at 120 h of treatment. **p21**-Cip1, which was very abundant in the ventral prostate of castrated and intact rats, was not detected when the prostate started proliferation and increased gradually as proliferation decreased during the androgen treatment. Meanwhile, **p27**-Kip1 dramatically increased after androgen treatment, and the induction levels were less at the peak of prostate proliferation and higher when proliferation was low. The results presented here suggest that expression of G1 cyclins and their related kinases and kinase inhibitors are well regulated after androgen replacement in the ventral prostate of castrated rats. The cooperation between these cell cycle regulators leads to a well-controlled prostate regeneration.

1996

20/3,AB/180 (Item 105 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10683322 BIOSIS NO.: 199799304467
Expression of cyclin dependent kinase inhibitors, **p21** and **p27**, during cardiac hypertrophy in rats.
AUTHOR: Li Jian-Mei; Brooks Gavin
AUTHOR ADDRESS: Rayne Inst., London**UK

JOURNAL: Circulation 94 (8 SUPPL.):pI551 **1996**
CONFERENCE/MEETING: 69th Scientific Sessions of the American Heart Association New Orleans, Louisiana, USA November 10-13, 1996
ISSN: 0009-7322
RECORD TYPE: Citation
LANGUAGE: English
1996

20/3,AB/181 (Item 106 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10606689 BIOSIS NO.: 199699227834
Changes in cell-cycle protein expression during experimental mesangial proliferative glomerulonephritis.
AUTHOR: Shankland Stuart J(a); Hugo Christian; Coats Steve R; Nangaku Masaomi; Pichler Raimund H; Gordon Katherine L; Pippin Jeffrey; Roberts James M; Couser William G; Johnson Richard J
AUTHOR ADDRESS: (a)Div. Nephrol., Univ. Washington, P.O. Box 35621, Seattle, WA 98195**USA
JOURNAL: Kidney International 50 (4):p1230-1239 **1996**
ISSN: 0085-2538
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A characteristic response to mesangial cell injury is proliferation, which is closely linked to mesangial matrix accumulation and the progression of glomerular disease. Cell proliferation in non-renal cells in vitro is regulated at the level of the cell-cycle by specific cyclins and their catalytic partners, cyclin dependent kinases (CDK). Cyclin kinase inhibitors (CKI) prevent proliferation by inhibiting cell-cycle progression. However, the expression of cell-cycle regulatory proteins in the kidney and in renal disease is unknown. To determine this we studied the expression of cell-cycle proteins in vivo in normal rats and rats with experimental mesangial proliferative glomerulonephritis (Thy1 model). Normal quiescent **rat** glomeruli have a differential expression for Waf1, Sdi1, Cap20) (**p21**) are low. The onset of mesangial cell proliferation in Thy1 glomerulonephritis is associated with a reduction in **p27**-Kip1 levels when mesangial cell proliferation is maximal. Mesangial cell proliferation in vivo is also associated with an increase in glomerular expression of cyclin A, and an increase in expression and activity for CDK2. The resolution of mesangial cell proliferation was associated with a return to baseline levels for **p27**-Kip1, while the expression for **p21** increased substantially. Furthermore, mesangial cell **p21** expression was maintained following the resolution of proliferation. These results provide evidence for a complex interplay of cell-cycle regulatory proteins during the glomerular response to injury in vivo. The marked increase in CDK2 expression during mesangial cell proliferation and the sustained increase in **p21** expression following the resolution of mesangial cell proliferation suggests that the in vivo expression of certain cell-cycle proteins may differ from that described in non-renal cells in vitro.
1996

20/3,AB/182 (Item 107 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10331652 BIOSIS NO.: 199698786570
Linking protein kinase C to the cell cycle: Ectopic expression of PKC-eta in NIH3T3 cells alters the expression of cyclins and Cdk inhibitors and

induces adipogenesis.
AUTHOR: Livneh Etta(a); Shi[redacted] Tova; Bechor Edna; Doki Yuich[redacted]; Schieren Ira; Weinstein I Bernard
AUTHOR ADDRESS: (a)Dep. Chem. Immunol., Weizmann Inst. Sci., Rehovot 76100 **Israel
JOURNAL: Oncogene 12 (7):p1545-1555 **1996**
ISSN: 0950-9232
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Protein kinase C encodes a family of enzymes implicated in cellular differentiation, growth control and tumor promotion. However, very tittle is known with respect to the molecular mechanisms that link protein kinase C to cell cycle control. Here we report that ectopic expression of PKC-eta in NIH3T3 fibroblasts blocks the normal phosphorylation of the Rb protein in quiescent cultures restimulated to enter the cell cycle; PKC-eta activates a cellular program that includes increased expression of cyclins E (but not cyclin D), as well as the induced expression of the cyclin-dependent kinase inhibitors **p21**-WAF1l and **p27**-KIP1. The increased expression of the latter inhibitors and their association with the cyclin ECdk2 complex results in decreased cyclin E associated kinase activity. Furthermore, in contrast to the control NIH3T3 cells, the cells that express PKC-eta can be induced to undergo adipocyte differentiation in response to adipogenic hormones. Thus, PKC-eta induces altered expression of several cell cycle related functions, which may contribute to its ability to promote cellular differentiation.

1996

20/3,AB/183 (Item 108 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10275141 BIOSIS NO.: 199698730059
Cyclin-dependent kinase inhibitor p57-KIP in soft tissue sarcomas and Wilms' tumors.
AUTHOR: Orlow Irene; Iavarone Antonio; Crider-Miller Shyra J; Bonilla Felix ; Latres Esther; Lee Mong-Hong; Gerald William L; Massague Joan; Weissman Bernard E; Cordon-Cardo Carlos(a)
AUTHOR ADDRESS: (a)Dep. Pathol., Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021**USA
JOURNAL: Cancer Research 56 (6):p1219-1221 **1996**
ISSN: 0008-5472
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Mammalian cyclin-dependent kinase inhibitors fall into two families, the INK4 and the CIP/KIP. The CIP/KIP family comprises three structurally related members, including **p21**-CiP1/WAF1, **p27**-KIP1, and p57-KIP2. These proteins are all capable of inhibiting the progression of the cell cycle by binding and inhibiting G-1 cyclin/cyclin-dependent kinase complexes. In humans, p57-KIP2 is expressed specifically in skeletal muscle, heart, brain, kidney, and lung. Human KIP2 resides in 11p15.5, a chromosomal region that is a common site for loss of heterozygosity in certain sarcomas, Wilms' tumors, and tumors associated with the Beckwith-Wiedemann syndrome. Because of the function, selective expression, and chromosomal location of p57-KIP2 we undertook the present study to search for potential mutations of KIP2 in a cohort of 126 tumors composed of 75 soft tissue sarcomas and 51 Wilms' tumors. The KIP2 gene was characterized by Southern blot, comparative multiplex PCR, PCR-single-strand

conformational polymorphis[redacted] and DNA sequencing assays in these neoplasms. Deletions of t[redacted]KIP2 gene or point mutations a[redacted]e region encoding the cyclin-dependent kinase inhibitory domain were not found in the tumors analyzed. The absence of KIP2 mutations might indicate that these tumors arise due to defects at a closely linked but separate locus. Alternatively, similarly to the **mouse** homologue, inactivation of KIP2 could occur via genomic imprinting.

1996

20/3,AB/184 (Item 109 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10221530 BIOSIS NO.: 199698676448
Withdrawal of differentiation inhibitory activity/leukemia inhibitory factor up-regulates D-type cyclins and cyclin-dependent kinase inhibitors in **mouse** embryonic stem cells.
AUTHOR: Savatier P(a); Lapillonne H; Van Grunsven L A; Rudkin B B; Samarut J
AUTHOR ADDRESS: (a)Lab. Biol. Mol. Cell., UMR 49 CNRS, LA INRA, Ecole Normale Superieure Lyon, 46 allee d'Italie, 6**France
JOURNAL: Oncogene 12 (2):p309-322 **1996**
ISSN: 0950-9232
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The expression of E and D-type cyclins, Cyclin-Dependent Kinase (CDK) 2 and 4, as well as CDK inhibitors **p21**-Cip1 and **p27** -Kip1 were examined during in vitro differentiation of **mouse** embryonic stem (ES) cells. ES cells cultured in presence of Differentiation Inhibitory Activity/Leukemia Inhibitory Factor (DIA/LIF) express very low levels of cyclin E/CDK2 complexes, p21-Cip1 and **p27**-Ki111 CDK inhibitors, while cylin D/CDK4-associated kinase activity is undetectable. Withdrawal of DIA/LIF, which induces differentiation, results in the progressive up-regulation of all. Up-regulation of D cyclins occurs through an increase in the steady-state levels of mRNA, concomitantly with the activation of Brachyury and Goosecoid, two early markers of mesoderm differentiation. Similarly, cells from the epiblast of the early postimplantation **mouse** embryo do not express any cyclin D/CDK4 complexes. These are progressively upregulated at gastrulation and early organogenesis. DIA/LIF-stimulated ES cells are not growth-arrested by overexpression of p16-Ink4a, a specific inhibitor of CDK4 and CDK6. We propose that the G1/S transition may be regulated by a minimal mechanism in **mouse** embryonic stem cells. Induction of differentiation triggers the establishment of a more sophisticated mechanism involving both cyclin D/CDK4- and CDK inhibitor-associated control of G1-phase progression.

1996

20/3,AB/185 (Item 110 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10197832 BIOSIS NO.: 199698652750
Nerve growth factor-induced growth arrest and induction of **p21** -Cip1/WAF1 in NIH-3T3 cells expressing TrkA.
AUTHOR: Decker Stuart J
AUTHOR ADDRESS: Parke-Davis Pharmaceutical Res. Div., 2800 Plymouth Road, Ann Arbor, MI 48106**USA
JOURNAL: Journal of Biological Chemistry 270 (52):p30841-30844 **1995**

ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Treatment of NIH-3T3 cells expressing human TrkA with nerve growth factor (NGF) resulted in a rapid cessation of growth. Cells stopped dividing within 24 h of NGF treatment and failed to divide as long as NGF was present, accumulating in the G-1 stage of the cell cycle. NGF caused a prolonged activation of mitogen-activated protein kinase relative to EGF. NGF treatment of cells greatly increased levels of the **p21**-Cip1/WAF1 protein, an inhibitor of cyclin-dependent kinases, without affecting levels of **p27**-KIP1 or p16-INK4. Levels of **p21**-Cip1/WAF1 remained elevated for at least 48 h following NGF addition. EGF had little effect on **p21**-Cip1/WAF1 expression in the same parental cells expressing the human EGF receptor. NGF treatment of cells completely inhibited the activity of the cyclin-dependent protein kinases CDK2 and CDK4. Inhibition correlated with a 10-20-fold increase in the amount of **p21**-Cip1/WAF1 complexed with CDK2 and CDK4. Levels of CDK2 and CDK4 were decreased following NGF treatment of cells; however, levels of cyclin E and cyclin D were increased. These data indicate that NGF can induce cell cycle arrest of NIH-3T3, perhaps through modulation of **p21**-Cip1/WAF1 levels. The data also show that distinct signals are generated by TrkA versus the EGF receptor in NIH-3T3 cells.

1995

20/3,AB/186 (Item 111 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10040629 BIOSIS NO.: 199598495547
Redistribution of the CDK inhibitor **p27** between different cyclin cntdot CDK complexes in the **mouse** fibroblast cell cycle and in cells arrested with lovastatin or ultraviolet irradiation.
AUTHOR: Poon Randy Y C; Toyoshima Hideo; Hunter Tony(a)
AUTHOR ADDRESS: (a)Molecular Biol. Virology Lab., The Salk Inst. Biological Studies, La Jolla, CA 92037-1099**USA
JOURNAL: Molecular Biology of the Cell 6 (9):p1197-1213 **1995**
ISSN: 1059-1524
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The cyclin-dependent kinase (CDK) inhibitor **p27** binds and inhibits the kinase activity of several CDKs. Here we report an analysis of the behavior and partners of **p27** in Swiss 3T3 **mouse** fibroblasts during normal mitotic cell cycle progression, as well as in cells arrested at different stages in the cycle by growth factor deprivation, lovastatin treatment, or ultraviolet (UV) irradiation. We found that the level of **p27** is elevated in cells arrested in G0 by growth factor deprivation or contact inhibition. In G0, **p27** was predominantly monomeric, although some portion was associated with residual cyclin A cntdot Cdk2. During G1, all of **p27** was associated with cyclin D1 cntdot Cdk4 and was then redistributed to cyclin A cntdot Cdk2 as cells entered S phase. The loss of the monomeric **p27** pool as cyclins accumulate in G1 is consistent with the in vivo and in vitro data showing that **p27** binds better to cyclin cntdot CDK complexes than to monomeric CDKs. In growing cells, the majority of **p27** was associated with cyclin D1 and the level of **p27** was significantly lower than the level of cyclin D1. In cells arrested in G1 with lovastatin, cyclin D1 was degraded and **p27** was redistributed to cyclin A cntdot Cdk2. In contrast to **p21** (which is a **p27**

-related CDK inhibitor and is induced by UV irradiation), the level of **p27** was reduced after UV irradiation, but because cyclin D was degraded more rapidly than **p27**, there was a transient increase in binding of **p27** to cyclin A cntdot Cdk2. These data suggest that cyclin D1 cntdot Cdk4 acts as a reservoir for **p27**, and **p27** is redistributed from cyclin D1 cntdot Cdk4 to cyclin A cntdot Cdk2 complexes during S phase, or when cells are arrested by growth factor deprivation, lovastatin treatment, or UV irradiation. It is likely that a similar principle of redistribution of **p27** is used by the cell in other instances of cell cycle arrest.

1995

20/3,AB/187 (Item 112 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09811951 BIOSIS NO.: 199598266869
P57-KIP2, a structurally distinct member of the **p21**-CIP1 Cdk inhibitor family, is a candidate tumor suppressor gene.
AUTHOR: Matsuoka Shuhei; Edwards Michael C; Bai Chang; Parker Susan; Zhang Pumin; Bladini Antonio; Harper J Wade; Elledge Stephen J(a)
AUTHOR ADDRESS: (a)Howard Huhges Med. Inst., Baylor Coll. Med., Houston, TX 77030**USA
JOURNAL: Genes & Development 9 (6):p650-662 **1995**
ISSN: 0890-9369
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Cyclin-dependent kinases (Cdks) are positive regulators of cell proliferation, whereas Cdk inhibitors (CKIs) inhibit proliferation. We describe a new CKI, p57-KIP2, which is related to **p21**-CIP1 and **p27**-KIP1 cntdot p57-KIP2 is a potent, tight-binding inhibitor of several G-1 cyclin/Cdk complexes, and its binding is cyclin dependent. Unlike CIP1, KIP2 is not regulated by p53. Overexpression of p57-KIP2 arrests cells in G-1 cntdot p57-KIP2 proteins have a complex structure. **Mouse** p57-KIP2 consists of four structurally distinct domains: an amino-terminal Cdk inhibitory domain, a proline-rich domain, an acidic-repeat region, and a carboxy-terminal domain conserved with **p27**-KIP1. Human p57-KIP2 appears to have conserved the amino- and carboxy-terminal domains but has replaced the internal regions with sequences containing proline-alanine repeats. In situ hybridization during **mouse** embryogenesis revealed that KIP2 mRNA displays a striking pattern of expression during development, showing high level expression in skeletal muscle, brain, heart, lungs, and eye. Most of the KIP2-expressing cells are terminally differentiated, suggesting that p57-KIP2 is involved in decisions to exit the cell cycle during development and differentiation. Human KIP2 is located at 11p15.5, a region implicated in both sporadic cancers and Beckwith-Wiedemann syndrome, a familial cancer syndrome, marking it as a candidate tumor suppressor. The discovery of a new member of the **p21**-CIP1 inhibitor family with novel structural features and expression patterns suggests a complex role for these proteins in cell cycle control and development.

1995

20/3,AB/188 (Item 113 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09809346 BIOSIS NO.: 199598264264
Cloning of p57-KIP2, a cyclin-dependent kinase inhibitor with unique domain structure and tissue distribution.

AUTHOR: Lee Mong-Hong; Reynisdottir Inga; Massague Joan(a)
AUTHOR ADDRESS: (a)Cell Biology Genetics Program, Howard Hughes Med. Inst., Memorial Sloan-Kettering Cancer Cent., **USA
JOURNAL: Genes & Development 9 (6):p639-649 **1995**
ISSN: 0890-9369
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Progression through the cell cycle is catalyzed by cyclin-dependent kinases (CDKs) and is negatively controlled by CDK inhibitors (CDIs). We have isolated a new member of the **p21**-CIP1/**p27**-KIP1 CDI family and named it p57-KIP2 to denote its apparent molecular mass and higher similarity to **p27**-KIP1. Three distinct p57 cDNAs were cloned that differ at the start of their open reading frames and correspond to messages generated by the use of distinct splice acceptor sites. p57 is distinguished from **p21** and **p27** by its unique domain structure. Four distinct domains follow the heterogeneous amino-terminal region and include, in order, a **p21/p27**-related CDK inhibitory domain, a proline-rich (28% proline) domain, an acidic (36% glutamic or aspartic acid) domain, and a carboxy-terminal nuclear targeting domain that contains a putative CDK phosphorylation site and has sequence similarity to **p27** but not to **p21**. Most of the acidic domain consists of a novel, tandemly repeated 4-amino acid motif. p57 is a potent inhibitor of G-1- and S-phase CDKs (cyclin E-cdk2, cyclin D2-cdk4, and cyclin A-cdk2) and, to lesser extent, of the mitotic cyclin B-Cdc2. In mammalian cells, p57 localizes to the nucleus, associates with G-1 CDK components, and its overexpression causes a complete cell cycle arrest in G-1 phase. In contrast to the widespread expression of **p21** and **p27** in human tissues, p57 is expressed in a tissue-specific manner, as a 1.5-kb species in placenta and at lower levels in various other tissues and a 7-kb mRNA species observed in skeletal muscle and heart. The expression pattern and unique domain structure of p57 suggest that this CDI may play a specialized role in cell cycle control.

1995

20/3,AB/189 (Item 114 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09767835 BIOSIS NO.: 199598222753
Assignment of the human **p27**-Kip1 gene to 12p13 and its analysis in leukemias.
AUTHOR: Pietenpol Jennifer A; Bohlander Stefan K; Sato Yuko; Papadopoulos Nickolas; Liu Bo; Friedman Cynthia; Trask Barbara J; Roberts James M; Kinzler Kenneth W; Rowley Janet D; Vogelstein Bert(a)
AUTHOR ADDRESS: (a)Johns Hopkins Oncol. Center, Molecular Genetics Lab., 424 North Bond St., Baltimore, MD 21231-10**USA
JOURNAL: Cancer Research 55 (6):p1206-1210 **1995**
ISSN: 0008-5472
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The **p27**-Kip1 (**p27**) gene encodes an inducible inhibitor of cyclin-dependent kinase activity. Using a murine **p27** cDNA as probe, we obtained a human cDNA clone and subsequently used it to isolate a genomic clone of this gene. The coding region of the human **p27** gene was contained in two exons. Both the amino acid sequence and intron-exon organization of **p27** were similar to those previously found for the related cyclin-dependent kinase inhibitor **p21**-Waf1 (**p21**). The **p27** gene was localized to

chromosome band 12p13 by a combination of somatic cell hybrid and fluorescence in situ hybridization analyses. The **p27** gene product is thought to control the leukocyte cell cycle and the 12p13 chromosomal band is known to be deleted in leukemias, suggesting that the **p27** gene may act as a tumor suppressor gene in leukemias. Although **p27** was found to reside in the minimal region of chromosomal loss in hematological malignancies, no mutations of **p27** were observed in leukemia samples. Haploinsufficiency of **p27** may confer a growth advantage to leukemia cells.

1995

20/3,AB/190 (Item 115 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09409917 BIOSIS NO.: 199497418287
Cloning of **p27**-Kip1, a cyclin-dependent kinase inhibitor and a potential mediator of extracellular antimitogenic signals.
AUTHOR: Polyak Kornelia(a); Lee Mong-Hong(a); Erdjument-Bromage Hediye; Koff Andrew; Roberts James M; Tempst Paul; Massague Joan(a)
AUTHOR ADDRESS: (a)Howard Hughes Med. Inst., Cell Biol. and Genetics Program, New York, NY 10021**USA
JOURNAL: Cell 78 (1):p59-66 **1994**
ISSN: 0092-8674
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We cloned **p27**-Kip1, a cyclin-dependent kinase inhibitor implicated in G1 phase arrest by TGF-beta and cell-cell contact. **p27**-Kip1 associates with cyclin E-Cdk2 complexes in vivo and in vitro, prevents their activation, and inhibits previously activated complexes, and **p27**-Kip1 overexpression obstructs cell entry into S phase. **p27**-Kip1 potently inhibits Rb phosphorylation by cyclin E-Cdk2, cyclin A-Cdk2, and cyclin D2-Cdk4. **p27**-Kip1 is highly conserved and broadly expressed in human tissues, and its mRNA levels are similar in proliferating and quiescent cells. **p27**-Kip1 has a region of sequence similarity to **p21**-Cip1/WAF1, the Cdk inhibitor whose transcription is stimulated by p53. A **p27**-Kip1 peptide corresponding to this region retains Cdk inhibitory activity. We suggest that cell contact, TGF-beta, and p53 all restrain cell proliferation through related Cdk inhibitors.

1994

20/3,AB/191 (Item 116 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08740170 BIOSIS NO.: 199395029521
Phenotypic progression of a **rat** lymphoid cell line immortalized by human T-lymphotropic virus type I to induce lymphoma/leukemia-like disease in rats.
AUTHOR: Oka Takashi(a); Sonobe Hiroshi; Iwata Jun; Kubonishi Ichiro; Satoh Hitoshi; Takata Masaru; Tanaka Yuetsu; Tateno Masatoshi; Tozawa Hideki; et al
AUTHOR ADDRESS: (a)Dep. Pathology, Kochi Medical School, Kochi**Japan
JOURNAL: Journal of Virology 66 (11):p6686-6694 **1992**
ISSN: 0022-538X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: **Rat** lymphoid cell[redacted]TARS-1, immortalized by cocult[redacted] with adult T-cell leukemia cells, were intraperitoneally injected into 65 newborn, inbred WKAH/Hkm rats. In most of the rats, tumor nodules were discernible 7 to 15 days after transplantation but were completely rejected within 5 to 6 weeks. Two rats with no tumor nodules exhibited gait disturbances and paralysis of the hind legs 3 to 4 weeks after transplantation. Histological and hematological examinations revealed that a lymphoma/leukemia-like disease had developed in one of the two rats, and the T-lymphoid cell line WLeuk-1 was established from peripheral blood mononuclear cells from this **rat**. When the WLeuk-1 cells were transplanted into newborn WKAH/Hkm rats, the animals died of a lymphoma/leukemia-like disease within several weeks after transplantation, in contrast to their rejection of the TARS-1 cells. Southern blot and karyotype analyses revealed that WLeuk-1 cells had retained the marker chromosomes and human T-lymphotropic virus type I (HTLV-I) integration patterns of the parent cell line, TARS-1. The additional specific chromosome abnormalities 3p+, t(12;13), and Xq+ were found in the WLeuk-1 cells. Moreover, the expression of HTLV-I structural proteins was slightly depressed in WLeuk-1 cells, while that of the transacting factors p40-tax and **p21**-x, but not that of **p27**-rex, was enhanced about fivefold compared with that in TARS-1. The transactivating function of p40-tax was intact in WLeuk-1, as evidenced by enhanced interleukin-2 receptor alpha chain expression. These results suggest that aberrant expression of HTLV-I regulatory genes and alteration of cellular genes were associated with the phenotypic progression of the WLeuk-1 cell line.

1992

20/3,AB/192 (Item 117 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

06723848 BIOSIS NO.: 000088033274
ANALYSIS OF GAG PROTEINS FROM **MOUSE** MAMMARY TUMOR VIRUS
AUTHOR: HIZI A; HENDERSON L E; COPELAND T D; SOWDER R C; KRUTZSCH H C; OROSZLAN S
AUTHOR ADDRESS: LAB. MOL. VIROL. CARCINOGENESIS, BRI-BASIC RES. PROGRAM, NATL. CANCER INST.-FREDERICK CANCER RES. FACILITY, FREDERICK, MD. 21701.
JOURNAL: J VIROL 63 (6). 1989. 2543-2549. **1989**
FULL JOURNAL NAME: Journal of Virology
CODEN: JOVIA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Structural proteins designated p10gag, p21gag, p8gag, p3gag, p27gag, p27gag, and p14gag from the C3H strain of **mouse** mammary tumor virus (MMTV) were purified by reversed-phase high-pressure liquid chromatography. The N- and C-terminal amino acid sequences and amino acid composition of each protein were determined and compared with the amino acids encoded by the proviral DNA sequences for the MMTV gag gene. The results show that each of the purified proteins is a proteolytic cleavage product derived from the predicted primary translational product of the gag gene (Pr77gag) and their order in Pr77gag is p10-pp21-p8-p3-n-**p27**-p14 (where n respresents 17 predicted residues that were not identified among the purified proteins). Purified p10gag lacks the initiator methionine and has a myristoyl group attached in amide linkage to the N-terminal glycine residue predicted by the second codon of the gag gene. The cleavage products are continuous in the sequence of Pr77gag, and the C-terminal residue of p14gag is encoded by the last codon of the gag gene. By analogy with other retroviruses, p14gag is the viral nucleocapsid protein, p10gag is the matrix protein, and p27gag is the capsid protein of mature MMTV. Proteolytic cleavage sites in MMTV

pr77gag bear a striking resemblance to cleavage sites in the gag precursors of D-type retroviruses, suggesting that these viral proteases have similar specifities.

1989

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Set      Items   Description
S1        7259   P21 AND (INHIBIT?)
S2        5082   S1 AND PY<2000
S3          65   S2 AND PLANT?
S4          61   RD (unique items)
S5           1   S4 AND TRANSGENIC?
S6        5017   S2 NOT S3
S7          54   S6 AND TRANSGENIC?
S8          38   RD (unique items)
S9        4963   S6 NOT S7
S10         73   S9 AND STEM?
S11        351   S9 AND BLOOD?
S12        410   S10 OR S11
S13        371   RD (unique items)
S14        221   S13 AND GENE?
S15          2   S14 AND EXPAND?
S16         27   S14 AND P27
S17          4   SP1 AND P27 AND (MOUSE OR RAT)
S18        313   P21 AND P27 AND (MOUSE OR RAT)
S19        248   S18 AND PY<2001
S20        192   RD (unique items)
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           351  S11
           410  S12
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           221  S14
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            38  S8
          4963  S9
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           351  S11
           410  S12
           371  S13
           221  S14
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Set      Items   Description
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S8          38   RD (unique items)
S9        4963   S6 NOT S7
S10         73   S9 AND STEM?
S11        351   S9 AND BLOOD?
S12        410   S10 OR S11
S13        371   RD (unique items)
S14        221   S13 AND GENE?
S15          2   S14 AND EXPAND?
S16         27   S14 AND P27
S17          4   SP1 AND P27 AND (MOUSE OR RAT)
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Set     Items   Description
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S8         38   RD (unique items)
S9       4963   S6 NOT S7
S10        73   S9 AND STEM?
S11       351   S9 AND BLOOD?
S12       410   S10 OR S11
S13       371   RD (unique items)
S14       221   S13 AND GENE?
S15         2   S14 AND EXPAND?
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S20       192   RD (unique items)
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S22      5239   S3-S20
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